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THE TWENTY-FIFTH MAUDSLEY LECTURE— HENRY MAUDSLEY: HIS WORK AND INFLUENCE.

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THE keen pleasure I felt when I was invited to deliver this lecture arose not only from the honour which it conferred, but also because it offered an opportunity to link again the lecture founded in Henry Maudsley's memory with the hospital which is the living witness to his wisdom and generosity. The first Maudsley Lecture was given by Sir James Crichton Browne, a contemporary and friend of Maudsley; the second was given at the Maudsley Hospital by Sir Frederick Mott, who had seen much of him during the last decade of his life. Since then very few of those called to give this lecture had had any personal contact with him, and it seems appropriate that now, a hundred years after Maudsley entered University College Hospital as an apprentice, when he has become for most of us a shadowy figure of the Victorian past, I should attempt to revive the memory of what he did during his life and consider how his work lives on after him—most of all in the hospital and school where I, and so many more, have the privilege of working. Before I do this I would like to recall that on the list of Maudsley lecturers there is the name of Edward Mapother, a man singularly close to Maudsley in temperament and outlook, who carried forward the Maudsley Hospital in the spirit of its Founder's intention, and who would have been ideally fitted, in the 1939 lecture entrusted to him, to deal with the theme I am entering upon; unfortunately the war and his failing health came between, and Prof. Mapother never delivered the lecture. Sir James Crichton Browne compared Maudsley with Mercier; I compare Maudsley with Mapother, and recognize that in each generation there are men of rare gifts, severe in self-discipline, with strong and consistent purpose, who, in psychiatry as in other fields, accomplish much good and leave behind a lasting memorial.

Henry Maudsley was born in 1835. He grew up in a notable time; "of all decades in our history, a wise man would choose the 1850's to be young in," says Mr. G. M. Young. The giants were on the scene: Faraday, Clerk Maxwell, Darwin, Lyell, Owen; Carlyle, Tennyson, Ruskin, Dickens, Matthew Arnold; Herbert

Spencer, J. S. Mill, Lecky ; and as many more. There was intense intellectual activity and material success, self-questioning also, and social and spiritual discontent. Maudsley, however, was not at first much exposed to this revolution of ideas. He was born on a farm in the West Riding of Yorkshire, not far from Settle in Ribblesdale, of a family of yeomen who had been settled there for two centuries and more. "My father was a stolid Tory all his life, and quietly fixed to old ways of thinking and doing. He once told me, when I rebelled against traditional custom, that what was good enough for my forefathers was good enough for me," he says in a fragment of autobiography, which the kindness of Dr. Henry Maudsley of Melbourne has put at my disposal. Maudsley paints a drab picture of his childhood, after his mother had died ; he attended the Giggleswick school, where "we had to construe the Latin and then repeat the appropriate rule from the Eton Latin Grammar without in the least understanding what the words meant. Similarly, in the upper school, besides arithmetic I went through a part of the first book of Euclid without any comprehension of the problems, learning the letters of the lines and angles by heart and repeating them offhand and instantly forgetting them. The little instruction which I obtained was probably not mainly due to the system there, but in part also to the fact that I was a dayboy who had to walk over two miles to the school and back daily in summer and winter, in rain and snow. It was a hard time, but use and no experience of anything better made it tolerable, as it does everything else. Still it was a succession of sombre and dreary years, for my father was so profoundly afflicted by my mother's death, to whom he was ardently attached, that his natural silence was increased and hardly a word ever passed between us boys and him except when absolutely necessary." There were, however, some enlivening people—his paternal uncle John, a wayward, philosophically minded, well-read man ; and his maternal aunt, Elizabeth Bateson, a philanthropist of the true Victorian breed, who conducted schools, and after a quarrel with the vicar of Bolton set up her own dissenting chapel at Kellett. "I owed more than I can reckon to her," says Maudsley, "for the poetry which she used to repeat to me, and I, having got it by heart, used to rush into the kitchen and declaim it to the servant. To that early and useful instruction I owe, I believe, any quality of style in my writings." It was this aunt, Elizabeth Bateson, who had him sent, when he was 14, to be a private pupil in the house of the Rev. Alfred Newth at Oundle. There his world opened out. His teacher was a good classical and mathematical scholar, widely read in general literature, who took him through Homer and the great Greek tragedians and historians, and, of course, the Latin writers : Thucydides and Tacitus made a lasting impression on the boy, and so did the "Prometheus Bound" of Aeschylus ; no doubt the theme of man's futile struggle against necessity, which recurs so often in Maudsley's writings, got something of its imprint from that tragedy of rebellious pride.

To University College Hospital Maudsley went in 1850, after he had matriculated ; he was apprenticed for five years to Clover, who was then the Resident Medical Officer. He tells us that he was self-assertive and stubbornly rebellious against all control, "as I have always been," and that he did not avail

himself of the opportunities the practice of the hospital afforded, so that Sharpey, the Professor of Physiology, remarked, "Maudsley has great abilities, but he has chosen to throw them into the gutter." Maudsley's terse comment is, "Happily I managed to pick some of them up again before they entirely rotted." His capacity for memorizing from books and for expressing himself well enabled him, he says, in spite of his wild courses, to gain a scholarship and a rouleau of gold medals. When he had his degree he designed to be a surgeon, but his lack of means and some trifling miscarriage of letters hindered him in this; so he decided to enter the East India Company's service. As they required their doctors to have spent six months in an asylum, he took a post as assistant medical officer at Wakefield, where he stayed nine months, and got on famously with his "congenial Yorkshire countrymen." From then there was no more talk of surgery or the East India Company; psychiatry had marked him for its own. A brief spell at Brentwood (where, I regret to say, he took a strong dislike to the people of Essex) was followed by a decisive event—his appointment as Medical Superintendent of Cheadle Royal.

He was only twenty-three, he had had no lengthy or formal training in psychiatry and no experience of administration, he had scamped his clinical studies, and he had vacillated in his career; his teachers did not think he was steady or tractable. What chance would he have had before a selection committee nowadays? What chance even of being "short-listed"? Those hard-headed Victorian committeemen in Manchester gave over the conduct of their new Royal Hospital for the Insane to this clever, headstrong, handsome young Yorkshireman. His success in the post was outstanding, and their courage and judgment bore richer fruit than they could foresee, and in a wider field. I think it is worth pausing to consider whether we are not in danger nowadays of becoming hidebound in our demands upon every aspirant, whatever his talents and promise; no doubt our requirements are the safe and right ones for the majority of candidates, but we have no great cause to preen ourselves on our skill in selection or our readiness to back a winner when we make comparison with our staid forefathers of a hundred years ago. To go no further than neurology and psychiatry. Hughlings Jackson, born in the same year as Maudsley, was on the senior staff of the National Hospital by the time he was 27, and of the London Hospital at 28; Griesinger, Maudsley's nearest counterpart in Germany, had, like him, neglected his regular classes as a medical student, had been self-willed and impatient of control, and had no more than two years' mental hospital experience when he published, at 28, his great textbook which radically influenced German psychiatry and made him its accepted leader. The range and content of psychiatry have been much extended in the last hundred years; but it is still, I think, true that a man of exceptional powers can acquaint himself in a few years of concentrated observation, reading and reflection with all the current knowledge he needs and can use, while the rest of us work our way steadily through the appointed stages of a lengthy training. If we force the Maudsleys and Griesingers of our day to delay their productive time until they have satisfied our normal and regular demands upon the would-be psychiatrist—and worse, until they have completed their "analysis"—I think psychiatry may suffer. Our difficulty, obviously, lies

in knowing how to distinguish between the slick, hasty smatterer claiming privilege, and the impatient man with an original mind, fertile, selective and independent.

I have called Maudsley's appointment to Cheadle Royal a decisive event. He stayed there only three years, but in that formative time he learnt to know his subject and himself in a way that had not been possible before. He set about the practical business of his charge with sense and energy, effecting many improvements and some enlargement; he thought deeply, read much and wrote profusely and experimentally, stretching his literary limbs. In these writings there is explicit statement of most of the ideas that were to occupy him for the rest of his life.

His three Annual Reports at Cheadle Royal (for access to which I am much indebted to Dr. Roy) exhibit a mature and conscientious outlook. In the first he emphasizes the importance of treatment early in the illness, and points out that the supposed causes of insanity in each case are by no means definite efficient causes, that there are commonly many partial causes or conditions of the disease, some predisposing, some exciting, and that "the bodily derangement which so commonly exists in cases of insanity cannot be always regarded in the light of a cause; it often partakes as much of the character of effect. The physical acts on the mental, and the mental back again on the physical, and vice versa—cause and effect acting and reacting, and mutually aggravating one another. The old rule that 'the cause having ceased, the effect ceases' is false almost as often as it is true; the effect often continues after the cause has ceased and, thus abiding, becomes in its turn a cause." Disturbance of the emotions and morbid introspection are the most conspicuous features of insanity—"the insane walks along, in many cases, the embodiment of an exaggerated emotion. . . . There is no boundary line between sanity and insanity; and the slightly exaggerated feeling which renders a man 'peculiar' in the world differs only in degree from that which places hundreds in an asylum. He who is eternally contemplating his own feelings can scarcely be pronounced to be perfectly sane"; exaggerated and distorted emotion leads to exaggerated and distorted ideas; if the ideas are lively and active, it is mania; if gloomy in character, it is melancholia. Hereditary predisposition is a most important cause, though often hidden by relatives who deny the facts: "Where hereditary predisposition exists, a cause so slight as to be inappreciable to observers is often efficient to produce the disease." As for treatment, he describes at length the many occupations and amusements which are arranged for the patients, and he denounces a "system which permitted to the insane only the monotony of a lifelong incarceration, and the inestimable privilege of wishing, like Hafiz, 'to break up the tiresome old vault of heaven into new forms'." In his report of the following year Maudsley refuses to classify as "recovered" those who were well when they left the hospital, but might not remain so, and he adds, as we might to-day, "a candid experience in the treatment of insanity must teach the wisdom of a discreet scepticism with regard to very high percentages of so-called recoveries." He remarks on the mild form of lifelong susceptibility to breakdown which makes the mental hospital a haven for some people: "it might seem a painful thing to deprive of liberty

persons who appear so little ailing, were it not that a repeated experience has shown it to be really a vain folly, if not a positive cruelty, to send them forth into the trials of life, when they are utterly unable to encounter them." He deplores the "strange, foolish and unjust prejudice" about insanity: "the slightest consideration would teach that an unavoidable affliction cannot be counted as a shame or disgrace." Heredity, again, receives much notice: he deplores the dysgenic consequences of women leaving hospital to conceive more children who may inherit the disease; and *à propos* of the frequency of insanity in unmarried people, he refers to the harmful postponement of the age of marriage, because civilization multiplies tastes and causes luxuries to be regarded as essentials of life. A discussion of will and the power of emotion foreshadows his later writings on free will and responsibility. Degeneration, as Morel understood it, and the "neuropathic taint" also begin to appear: "inherited weakness of any kind, unless there has been the compensation of a good education and a happy collocation of circumstances, must be exhibited in some form of weakness or other, whether it be as drunkenness, crime, immorality or insanity. . . . Families, like trees, often grow till they have attained their greatest development, then begin to decay, and ultimately die out." He reverts, in the tones of a preacher, to the theme "that it is a grievous mistake to neglect the formation of character as an aim of existence"; when he dilates on this the future sceptic is out of sight, and the yeast of authentic Victorian earnestness is at work. In this report, as in the previous one, he shows a close acquaintance with the classical text-book of Esquirol. His last report, much briefer, in 1861, makes two cardinal points: First, that on no account should lies and stratagems be used to get the patient to hospital; secondly, that mental disorder is to be considered an illness, not a visitation—"truth has as much force with the insane as with the sane, and it would seem to be the simple right of those who are afflicted and need control, that they should have the truth spoken to them"; moreover, "in place of the sufferer being sent to the hospital with the utmost secrecy as if some great disgrace were to be concealed, he is sent distinctly for the medical treatment of a disease, just as he would be placed under medical care for any other bodily disease." You will notice that word "other"—much of Maudsley's thought and writing was devoted to maintaining that insanity is a bodily disease.

I have dwelt upon these reports because they show us, so early in his life, Maudsley the psychiatrist, humane, practical, honest and outspoken, voicing in 1860 opinions which still in our day have to be asserted, which indeed many people suppose to have been unthought of until our generation asserted them.

Alongside Maudsley the psychiatrist there was then, and for the rest of his life, Maudsley the philosophic inquirer; Maudsley the positivist, to whom metaphysics was anathema. It is in the nature of our subject that every thoughtful psychiatrist can choose only between having his philosophic standpoint explicit or leaving it implicit; a philosophic standpoint of some sort he must have. Consequently the problems that troubled Maudsley are the perennial basic problems of us all. His views on them are inextricably woven into the fabric of his psychiatry, but his approach is that of his time and—need it be said—of his personality.

The first article of his that was published was on the "Correlation of Mental and Physical Force, or, Man, a Part of Nature," which appeared in October, 1859, in the *Journal of Mental Science*. It said substantially about metaphysics what he was still saying in "Organic to Human" nearly sixty years later—that man's consciousness and moral nature and all his other psychological attributes are closely dependent on the physical structure of his brain. Much influenced by Grove's recent book on the correlation of physical forces, Maudsley argued, with skill and fervour, that the same continuity exists between mental and physical as between the various sorts of physical force; he inveighed against man's vanity in measuring himself against and apart from the rest of nature, his abuse of the power to see things in words, and his propensity "to ignore himself as a material being and to speculate loosely and dilate rapturously on his mental being." Metaphysics, says Maudsley, is the vanity of vanities, its study a vexation of spirit, because it concerns itself not with phenomena but with the hypothesis of essence. He regrets, moreover, that "so eminent a philosopher as Auguste Comte should be one of those who have endeavoured to place science and religion in antagonism to one another." Repudiating "pure materialism," he glances at the universe in its gradual evolution, in which mind appears as one of the sequent effects in its due time and season, and he concludes that all forces are "but modes of manifestation of one force—the Will of God—manifest in highest form and with least obscuratation in the temple of man's body."

This young philosopher and medical superintendent, who freely quotes Mill and Faraday, Spinoza and Leibnitz, St. Paul and Shakespeare, was the child of his time. In the late eighteen-fifties man's place in nature was a topic uppermost in the minds of thinking men. The conflict between the evolutionists and theologians like Bishop Wilberforce was already joined, though, of course, the *Origin of Species* had not yet been published and only a précis of Darwin's manuscript had been read before the Linnaean Society. Herbert Spencer had expressed in his *Principles of Psychology* a genetic and materialist view, rather loosely formulated, of the mind and its significance in evolutionary progress through differentiation, and he had objected to the hypothesis of special creation of species, just as Maudsley after him objected to the hypothesis of special creation of consciousness and moral feeling. Other influences producing the intellectual and spiritual turmoil of that generation were to be found among the philosophers—Sir William Hamilton, James and John Stuart Mill, Bain, W. A. Carpenter, Mansel. The Germans Schelling and Herbart, and the French physiologist-philosophers like Cabanis and Bichat, also exerted indirect influence and were closely read by Maudsley.

There is little, I think, in that first essay of Maudsley's that is not to be found in other writings of the time; what is significant is that here was a young psychiatrist well versed in the great argument, bold and confident enough to take a stand which compelled the attention of philosophers, and evidently determined to carry these vigorous principles into his study of morbid as well as normal mental states and activities. He had not defined his position rigorously or consistently, as Croom Robertson and Stout sharply pointed out when examining his views some years later; his version of positivism (shorn

of ritual and ethic) seems to have been, not philosophy acting in the service of natural science, to use R. G. Collingwood's phrase, but rather natural science acting in the service of psychology; and he attacks metaphysics with some of the metaphysicians' own weapons—a dangerous venture, but the Maudsley of the *Physiology and Pathology of Mind*, of *Natural Causes and Supernatural Seemings*, of *Responsibility in Mental Disease*, was clearly presaged in the article by this audacious newcomer of 1859.

In 1860 he published two articles, both dealing with literary genius; one of these, much influenced in content and style by Carlyle, is about Edgar Allen Poe; the other examines discursively the insanity of many a famous man, and in one passage foreshadows Maudsley's treatise on psychiatry—"this must be the aim of a philosophical history of madness, should it ever come to pass that such an one is undertaken, a history which should aspire to establish some principle or principles but which, at any rate, should not be content to occupy itself with a catalogue of appearances. . . . In an account of insanity in any form there are thus two elements to be taken into consideration, one almost as important as the other; these are the subject and the environment, the man and his circumstances, subjective force and objective forces, both passive and active; and the problem for solution is, what there was in the one or in the other whereby harmonious co-operation between them became impossible and a discord was, of necessity, produced. . . . materials (for a general history of insanity written in a philosophical spirit) lie in profusion around every one who has devoted himself to the care and treatment of the insane." In this essay, testifying in its gusto and exuberance to its author's comparative youth, he expresses a young man's conclusion—that "the act of dying is generally very agreeable." It is noteworthy that shortly before his end, as a tired old man of 81, solitary and disillusioned, he repeated this belief in much the same language, in the characteristic essay on "Death" that appeared in *Religion and Realities*. His account of various eccentrics in the 1860 essay is delightful in its tolerant enjoyment of absurdities; for example, his story of Thomas Wirgman, the philosophical goldsmith, who persuaded the Guardians of St. Pancras to allow him to try out on the pauper children his system of metaphysics, which was to bring universal peace and virtue on earth by teaching a "grammar of the five senses."

In the next year Maudsley, no doubt stimulated by the fierce controversy between Owen and Huxley, wrote a learned and elaborate article on the "Genesis of Mind," in which the problems of cerebral development are surveyed. It is notable for the plain indications of Herbert Spencer's influence, and for its more than Tennysonian confidence in man's upward progress; as for the former, one can understand Herbert Spencer's petulance in his letter to Tyndal in 1868, wherein he complained at Maudsley's barely acknowledged but heavy indebtedness to him. Maudsley's confidence in man's future, expressed with a simple and—to our embittered view—naïve faith, is startling, coming from a man who is now remembered as a pessimist. In 1860 all is for the best in the evolutionary survival of the fittest; the degenerate and the primitive are being eliminated as "humanity, in its progress upwards, fashions the supporting stem only by sacrificing the early branches. All observation

proves that mankind is advancing. The beings of the present civilization are evidently superior to those of any past civilization, and the beings who now make barbarism appear to be disappearing from the earth." "When we reflect that moral principles are not merely intellectual speculations but actual laws of nature, as certain and uniform in their operations as are the physical laws there is every reason to anticipate that, as the recognition of the physical laws, has added so greatly to the power and comfort of mankind, so the practical realization of the moral laws in the conduct of life will increase the happiness, advance the mental development and, perhaps, insure the stability of nations." "In place of degeneration and destruction from ignorance of, and disobedience to, the physical laws, there are development and salvation from knowledge of, and obedience to, them. . . . As soon as ever men have attained to a sincere, intellectual recognition of the causes and laws of events, there inevitably springs up the correlative moral cognition. . . . We have a certain guarantee of moral progress." "Love and virtue must replace cruelty and vice: that . . . simple scientific observation of the natural course of the development of mind compels us gladly and confidently to anticipate; it is the realization in general practice of those sublime principles which revelation has inculcated. And such, happily, will be the functional expression of the superior type of brain amongst modern civilized nations." "Advancing knowledge is becoming conscious of the love that there is in every apparent evil. In fact, the wider and deeper our insight becomes, the more clearly do we perceive love working in every event of nature, all-embracing, all-supporting, all-powerful." These millenarian rhapsodies are strange; Maudsley was no Pangloss, nor was he writing a Bridgewater treatise, but he echoed the hopes of his time; and he was not the first to base his assurance of Utopia upon a pessimistic view of man's past state, from which a rational progress should henceforth redeem him. The development of this notion of progress in the nineteenth century, the confusion between the biological conception of progress through natural selection and the humanistic conception of it through the working of man's moral nature; the contrast, superficial but striking, between the optimists and the pessimists; the struggle to relate, if not to reconcile, religious with biological views of man's past and future—these are familiar to us in the pages of Ruskin and Carlyle, Herbert Spencer, Mill, and many more of the noted men of that time. Darwin himself wrote, at the conclusion of the *Origin of Species*: "As natural selection works solely for the good of each being, all corporal and mental environment will tend to progress towards perfection." I need not stress further the obvious similarity between Maudsley's views and those which agitated or comforted his generation, but his profession gave a special bias to his statement of these views and later led him away from them. He wrote, when he was 60, "a physician who had spent his life in ministering to diseased minds might be excused if, asking himself at the end of it whether he had spent his life well, he accused the fortune of an evil hour which threw him on that track of work. He could not well help feeling something of bitterness in the certitude that one half of the disease he had dealt with never could get well, and something of misgiving in the reflection whether he had done real service to his kind by restoring the other half to do

reproductive work. Nor would the scientific interest of his studies compensate entirely for the practical uncertainties, since their revelation of the structure of human nature might inspire a doubt whether, notwithstanding impassioned aims, paeans of progress, endless pageants of self-illusions, its capacity of degeneration did not equal, and might some day exceed, its capacity of development." That is a profoundly disillusioned, unhappy conclusion. It would be easy to read into it an unrelieved pessimism, but in later writings of his we find again qualified optimism, weighed against qualified pessimism; scepticism rather than despair. There were, as Maudsley himself maintained, two warring strains in him: "I have always thought and said," he wrote in his autobiography, "that the paternal and maternal were never vitally *welded* in me, but only *riveted*." He was, he tells us, in his youth self-assertive, but at the same time a tormenting critic of himself. His friends described his "difficult personality, his tart replies and scathing judgments," while they recall also his "genial look and friendly interest." He was, indeed, by no means a sociable, affable doctor, full of the team-spirit, who would demonstrate to the world that the psychiatrist is a good fellow; but he was not a Timon or Thersites either. He recognized the vigorous intrinsic animality in human beings, while he abhorred its manifestation in cruelty and deceit. As he grew older he took it more and more for granted, though he never quite reconciled the moral aspiration that had been so strong in his youth and was still quick in him as an old man, with the resigned, half-doubting meliorism that represented his final standpoint as philosopher-psychiatrist.

The warring strains in him, which he attributed to the intellectual tough-minded inheritance from his father and the emotional, religious warmth from his mother, asserted themselves in other views that appear often in the writings that stretch over sixty years. He denounced introspection and metaphysics, yet he constantly returned to the metaphysical problem of the mind-body relationship, which fascinated him (as it has always fascinated psychiatrists); he inveighed against the tyranny and deceit of words, especially of newly invented words, but he laboured to be eloquent and he proposed new coinages (such as "paramorphic" and "boulepsy"); he was a Positivist who rejected the ritual and religion which was the mainspring of Comte's teaching; he detested the brutishness, and worse than brutishness, men can display, yet he extolled war in language that shocks us: "War in one shape or another, open or disguised, has plainly been the divinely appointed instrument of human progress, carnage the immoral-seeming means by which the slow incarnation of morality in mankind has been effected"—we have to remind ourselves that this also is the language of Tennyson's Maud, that it was commoner, and certainly easier, then than now for war to be misconceived as a heroic and beneficent instrument of natural selection. There are other contradictions evident in his writings, but these, so far from indicating weakness, bespeak, I believe, Maudsley's criticism of doctrines prevailing in his time—doctrines which he espoused, it is true, and which he enriched from his experience as a psychiatrist; but this very experience and the tenacity and candour of his mind compelled him to doubt their general application. In some matters on which he wrote he was no wiser than his generation, but his chief inconsis-

tencies bring him closer to modern views than a consistent adhesion or opposition to the opinions of his time—I mean the period between 1860 and 1890—would have permitted. This is illustrated by his views about the pathology of mental disease, which I shall mention presently.

It is well, moreover, to remember that Maudsley was fond of contrasting the two types of creative mind; thus in 1866 he wrote that the men who influence mankind fall into two classes—"men of wide intellectual grasp, vast wisdom and serene energy; and the men of limited vision, intense feeling, and impetuous energy"; thirty years later he is more biting about the second class—"persons who are clever but flighty, talented but unstable, intense but narrow, earnest but fanatical; all sorts of persons who, plunging into new movements, good or bad, and pursuing them with intemperate, perhaps dis-tempered, zeal, lack the just balance of the faculties, the calm equilibrium of a stable mental organization, the true proportion or mean of nature which is the highest sanity. In the end the result is some such misproportioned incongruity as the philanthropic zealot, reeking of self, whose testimony or character no prudent man of the world could trust, or the intensely neurotic investigator, aspiring to be scientific, who, seeing nothing else, is utterly untrustworthy as an observer." In his latest book, written shortly before his death, he returned to the theme: "The plain truth is that the pessimist observes sincerely, thinks fully and feels deeply. . . . Pessimism is alike the stern conclusion of thinking reason and the pious confession of reverent religion. . . . Optimism, on the other hand, is the practical expression of unthinking feeling." There can be no doubt that he knew himself to belong to the more mournful company, though sometimes feeling the energy and often enjoying the faith and exultant vitality of the optimists.

The writers whom he most often quotes are significant: Goethe perhaps more than any other; Shakespeare, the Bible (especially Ecclesiastes and Isaiah), Milton, Bacon, Pascal, Montaigne, Robert Burton, Sir Thomas Browne, Gibbon, Amiel; and of philosophers, Locke, Hobbes, Hume, Hamilton. These are lofty minds, often of a sombre and sceptical cast, like his own. Then there are the medical and scientific authors with whom he was evidently familiar: Darwin, Huxley, Carpenter, Laycock, Prichard, Brown-Séquard (but he never quotes Galton, and seldom Hughlings Jackson, though he and Jackson were both close to the thought of Herbert Spencer and had other things in common, including their Yorkshire origin; perhaps Hughlings Jackson's fear and contempt towards the mentally ill, which Savage noted, rather alienated Maudsley, who felt a close and sympathetic kinship with the insane). With the German and French writers of his middle life he was as familiar as with his English contemporaries; but he seems not to have kept up his psychiatric reading after the eighties and nineties as much as his general reading (which included Karl Marx's writings).

I come now to Maudsley as physician and psychiatrist. He had a high conception of what a doctor's life should be, and it would be hard to find a more outspoken panegyric of the value and opportunities of our profession than that contained in his introductory lecture delivered to the medical students at University College, London, in 1876, while he was Professor of Medical

Jurisprudence there. Throughout his life he tried to keep abreast of clinical and scientific developments, as his 1905 British Medical Association Lecture in Medicine showed; indeed his familiarity with then recent developments in physics is startling to a reader to-day; he stresses, for example, the importance of the demonstration that matter can be resolved into moving electric charges, and he says, "a living cell seems but a gross thing. Concentrated within its little body are subtle and intense forces continuously and quietly working which, if let loose in large explosive display, might suffice to blow up the chemist and his whole laboratory." It is his psychological rather than his general medical and scientific standpoint that is chiefly of interest to us.

Maudsley entered psychiatry at a time when the prestige of English and Scottish philosophers stood high throughout the learned world for their psychological speculations, and when British psychiatrists enjoyed very little regard outside these islands; Pinel's strictures upon them had not been lived down, and only J. C. Prichard's writings and Conolly's had attracted some attention or excited controversy abroad. When the young Maudsley in 1867 published his *Physiology and Pathology of Mind* it was promptly acclaimed by Westphal, in Griesinger's new journal, as the most important psychiatric work to appear in that year, one which he hoped might long exercise an influence on our science. Similarly, Ribot gave the book warm but discriminating praise a few years later, by which time it had been translated into German, Italian, French and Japanese. Henceforward, until well within this century, few of the most prominent psychiatrists of other countries failed to show some acquaintance with Maudsley's writings and views, either on psychiatry in general or on those special questions of psychosomatic relations, criminal responsibility in mental disease, and the psychology of "supernatural seemings" to which he had devoted particular books. Although Bucknill, Daniel Hack Tuke, Clouston and some others later became known abroad, it was Maudsley that taught German and French psychiatrists that they could not safely disregard everything in our psychiatry except "no restraint." I think the same may be said of the Italian psychiatrists, but I know too little of them, apart from Lugaro and Tanzi, to be sure. At all events, the publication of *Physiology and Pathology of Mind* was a turning point in English psychiatry; it presaged the end of the period in which psychiatry rested on a magma of empirical observations and windy philosophizing, and it embodied a critical synthesis of biological and other scientific advances so far as they had an evident bearing on mental activity, in health and disease. Moreover, it took account of what the French and the Germans were then so vigorously contributing to psychiatric theory and observation. I would not like to give an impression that Maudsley appeared a giant among the English pygmies; I have been convinced in reading those early volumes of the *Journal of Mental Science* that in the Association of Medical Officers of Asylums and Hospitals for the Insane there was as much capacity and erudition as might be found now in a much larger circle of our members, and perhaps more vitality than is commonly exhibited in a professional association when it has become large and prudent. Only an arrogant and ill-informed psychiatrist in our day would look down on the men who contributed to the advance of our subject in the mid-Victorian period. But

though these contemporaries of Maudsley were men of considerable stature, they had not the grasp, the acumen and the facility of expression which made his work outstanding and potent. He had something important to say on many topics that are fundamental for psychologists and psychiatrists, and he said it insistently, pointing to recent discoveries and, still more, to some recent and old absurdities which were, in his eyes, strangling progress.

On these matters he felt so strongly that he wrote intemperately. His attacks on introspection were violent, beyond what he could justify in his later writings; but he was battling less against introspection and metaphysics in psychology than against that irrational dualism which denied that mental activity could be studied by the scientific method on the ground that it was exempt from any laws of predictable succession. Hence his diatribes, and his vehement assertion that psychology was cerebral physiology. Hence also his lifelong concern with the problems of will in disease and crime. As early as 1863 he had shown his bitter indignation at the way popular clamour and legal pedantry could cause a manifestly insane murderer to be hanged, and he could never stomach the argument that man has a dual composition—body (including brain) acting in a way determined by its structure and history, and mind, which, having free will, is to be judged and held accountable quite otherwise than as the body is.

This is the place to consider Maudsley's view about consciousness—obviously a crucial issue in his campaign against dualism. Briefly, he held that consciousness is the adjunct of mental function, merely lighting up a small part of the mental process; never preceding or dictating a mental occurrence, but only accompanying it or following it. The motives of behaviour "are very mixed, and their main work is unconscious." He was, of course, familiar with the views of von Hartmann, Schopenhauer, Beneke and other philosophers on this matter, and in his insistence from the beginning on a wholly physiological psychology he took account of the difficulties which the fact of consciousness had presented to these writers. He never succeeded in resolving the problem—who has?—but his standpoint about consciousness was, in essence, not different from that of, say, Lashley, allowing for the vast disparity in the relevant knowledge available to the two men. His constant stress upon the immense importance of the processes that occur unconsciously has led a psychoanalytic writer, Christoffel (to whose essay Dr. Stengel directed my attention), to claim him as in some sort a forerunner of psychoanalysis. I do not think the claim can be sustained. "Unconscious" was for Maudsley a negative psychological term of description; he applied it to cerebral happenings which in his view provided the whole dynamic of mental life, in contrast to the small segment of those cerebral happenings illuminated by consciousness, which the much-aborred metaphysicians liked to study by introspection. As soon as some of his contemporaries attributed to "subliminal consciousness" a mental force and quality of its own, he was up in arms; he called it a signal example of clever beguilement by words, and jeered at this "subliminal consciousness which can do marvellous things—as well indeed it may, being a positive consciousness, created out of negation, . . . a something which is and is not at the same instant." There can be no doubt that the Freudian conception of

the Unconscious was alien to Maudsley's thought, though it should be said that in many respects he was in sympathy with the psychoanalytic attitude; he constantly stressed the animality of human beings, their control by forces which they denied or ignored, their inner conflicts, the power of unsuspected or curbed sexuality (especially in women) and the passionate urges of the child. On the last matter his words may be quoted: "Whoever observes sincerely what a child's actual mind is, without being biased by preconceived notions of its primal purity, innocence and natural inclination to good, must see and own that its proclivities are not to good but to evil, and that the impulses which move it are the selfish impulses of passion. Give an infant in arms power in its limbs equal to its passions, and it would be more dangerous than any wild beast."

It would be impossible in this lecture to set out the chief features of Maudsley's clinical and theoretical psychiatry. I can only say that I have compared his book with Kraepelin's, published at about the same time (Maudsley's third edition and Kraepelin's second), and Maudsley's does not suffer by the comparison, though there are very wide differences in style and method: Kraepelin's is a text-book, Maudsley's a treatise. It would be a most valuable formative experience even now for young psychiatrists of ability to read Maudsley's major works; there they would meet a powerful critical intellect, versed in clinical practice, impatient of shams, and capable also of fertile synthesis. Maudsley's originality appears in his assertion of opinions, then heterodox, and even now fancied by many to be banners first inscribed and flown in our own enlightened day. I will mention a few of these. He maintained that the psychosomatic relation is a reciprocal one occurring within a complex but unified organism, "each part of which calls the furthest brother, which acts upon the rest of it and is reacted on by it." He emphasized that emotion affecting every part of the body is "rooted in the unity of organic life," and he asserted that "it is in the natural order of events that continuance of perverted function should lead to organic disease." He required that treatment should be adapted to the particular patient—"always the rule of rules should be to treat an individual who is sick, not an abstract disease." Narcotic drugs should be used with the greatest restraint. He rejected the claim of men like Schroeder van der Kolk to have discovered in the morbid anatomy of the brain the pathology of mental disease. "The morbid anatomy of insanity," he wrote, "would take little room were speculation rigidly excluded and it limited to what is actually seen and known. Nor does that which is seen, it must be confessed, throw much light on the symptoms. . . . The intimate chemical and molecular changes which are presumably the conditions of mental disorder go on in a domain of nature the subtleties of which far exceed the subtleties of observation." In another remarkable passage he suggests that it might be easier to conceive what nervous disorder means if, "instead of thinking of the body as a material structure built up of so many organs, one were to abolish in imagination the gross matter, to think it clean away, and to conceive its organs as so many and divers complexes of very fine and active vibrations bound within the forms and shapes of the different organs and united by the most complete harmony of inter-nuncial vibrations, the whole organism

being the formal unison of these multitudinous and various complexes of energies." In all his writings on this theme, even where he falls (like every medical writer of his time who dealt with it) into "brain mythology," he displays a prescient imagination; thus, in melancholia (for which no one had then suggested leucotomy) he speculated about the "exorbitant and predominant, almost exclusive, activity of certain brain tracts charged with sad feeling"; and in mania he guessed that "the functions of the most fine and special tracteries of the cortical reflexes are suspended or effaced, being too delicate to lend themselves to the currents of turbulent energy which now pass along coarser channels." Crude as these surmises are, they are perhaps no cruder than those will seem in fifty years which now, to us, represent the striking discoveries recently made in cerebral physiology, applied to the problems of mental disease. Still, these opinions of Maudsley's are at best speculations, unsupported by any evidence. Where he dealt with more substantial matters, Maudsley again strikes us as an anticipator of our practice. He even suggested, in his Goulstonian Lectures in 1870, that if we had the power to induce general convulsions in some cases of acute insanity, "we might, for the time being at any rate, cure the insanity." Not only in his precepts for treatment but in his general approach there is much that psychiatrists of our generation consider it important to reiterate. He emphasized the need for a full, searching life-history of the patient; causes are multiple, the notion of cause itself needing reconsideration and restatement; inherited predisposition is the most potent influence, but the actual outbreak of illness depends on whether circumstances of upbringing and subsequent life have been propitious or unpropitious; patients have often had the ill-fortune to be twice penalized, first in a bad inheritance, and secondly in a bad training given them by those who gave them that inheritance; there must therefore be "close and diligent study of the particular qualities of individual character, mental and bodily, and an exact exposition of its relations to its circumstances . . . a patient unfolding of (the person's) action on circumstances and of their action on him." The effect of circumstances, acting on a suitable inheritance, may be not insanity, but a lesser mental deformity or nervous obliquity, or it may be crime; crime "is clearly sometimes the result of an actual neurosis which has close relations of nature and descent to other neuroses."

There is a further topic to be mentioned among the many which might be taken to illustrate Maudsley's expression of views now sometimes trumpeted as up-to-date corrections of the unwisdom of our predecessors—it is classification. I single it out because Dr. Gregory Zilboorg, in his erudite *History of Medical Psychology*, has been severe upon Maudsley in this particular. He says that "the classificatory effort of Maudsley appears unenlightened; were it not for his insistence on careful historical studies of each individual patient, one could not easily discern the human being behind the classificatory frame," and he says that Maudsley was "purely materialistic and purely descriptive"—a remark often made nowadays about Kraepelin too. As early as 1859 you will recall Maudsley had written that "a philosophical history of insanity . . . should not be content to occupy itself with a catalogue of appearances." In his *Pathology of Mind* he followed at first, with patent misgivings, the classi-

fication of Esquirol ; he was critical of Skae's ambitious scheme, though recognizing the practical if limited usefulness of singling out mental diseases regularly associated with a bodily disease ; and he similarly appraised Morel's scheme of classification. The note on classification in the second edition, 1868, states his very reasonable position. In 1879, in the third edition, he gives a brief, clear explanation of his grounds for adhering, for the present, to a simple symptomatological classification ; " this necessity of calling up by a general term the conception of a certain co-existence and sequence of symptoms is a reason why the old classification holds its ground against classifications that are alleged to be more scientific ; it is good as far as it goes, but it by no means goes to the root of the matter ; whereas the classifications which pretend to go to the root of the matter go beyond what knowledge warrants and are radically faulty." Finally in 1895 he says quite explicitly in the Preface, " A leading aim through (the work) having been to clear the ground by endeavouring to think the subject into simplicity and to set forth the results in as plain language as possible, I have purposely avoided mention of the numerous and elaborate classifications which, in almost distracting succession, have been formally proposed as exhaustive and tacitly condemned as useless. For the same reason I have shunned the use of the many learned names—of Greek, Latin and Graeco-Latin derivation—which have been invented in appalling numbers often to denote simple things and sometimes, it may be feared, with the effect of confounding apprehension of them. Insanities are not really so different from sanities that they need a new and special language to describe them ; nor are they so separated from other nervous disorders by lines of demarcation as to render it wise to distinguish every feature of them by a special technical nomenclature."

I have dealt a little more fully with this matter than its intrinsic importance warrants, but as Dr. Zilboorg has been so damning in his main comment on Maudsley, largely on the score of his classificatory procedure, I thought it proper to clear the issue, in the hope that Dr. Zilboorg in subsequent editions of his justly esteemed book will give due recognition to Maudsley's outstanding merits among nineteenth century psychiatrists.

So far Maudsley appears as the brilliant iconoclast, the erudite reasoner who could expound lucidly the principles of physiological psychology, the sage, the far-sighted writer on clinical psychiatry. His influence, in spite of his unsociable ways, was immense, and was not limited to the narrow circle of psychiatrists and psychologists ; Darwin, for example, quoted Maudsley frequently in the *Descent of Man* and in the *Expression of the Emotions*. Professor Boring, of Harvard, the discriminating historian of experimental psychology, wrote in 1929 that the first edition of Maudsley's *Physiology and Pathology of Mind* was a " very influential book which forms the background for the tradition for medical psychology in Great Britain." I need not amplify such a judgment or look closely into the indirect means whereby Maudsley's influence extended beyond the range of those who knew him or read his books. It is clearly also difficult or impossible to separate his influence from that of precursors and contemporaries with whom he had much in common ; still more difficult to separate or trace it in successors who have incorporated his views along with

much knowledge which was not available to him and many opinions which would have astounded him. It might therefore be assumed that his influence, though great in his active period, became steadily less manifest and less potent as the decades passed. If his works had consisted solely of his writings and clinical activity, that would be so, and he would now be a fading, Victorian figure, no better known to the psychiatrists of a later day than, say, Hack Tuke, Magnan or Kahlbaum. But Maudsley, the sceptic, the childless pessimist, decided upon a constructive act which would project his intention further than books or talking could; he created a living organism, to be his heir. The steps he took have been described by Sir Frederick Mott, who acted as go-between in the drawn-out negotiations between Maudsley and the London County Council that started in 1907, but the genesis of the project lay further back. While he was at Cheadle Royal Maudsley had urged the need for early treatment. Then, in his early days as a rising consultant in London, he had evolved plans for such early treatment in concert with that earnest champion of family care, "my friend Baron Mundy, M.D., of Moravia," and others of Maudsley's circle, who used to meet (as Crichton Browne tells us) at a Soho restaurant to discourse about the future of psychiatry and the betterment of mankind. I had supposed these plans of Maudsley's to be pioneer efforts until I chanced upon the paper in which Samuel Gaskell, in 1860, when he had become Commissioner in Lunacy, advocated voluntary treatment, free from legal forms, so that remedial measures might be instituted early and for a class of patient, with mild forms of disorder, who would not "resort to asylums as at present constituted." Maudsley must have read this paper with conviction, and still more he must have been impressed by the reiterated views of his father-in-law, Conolly, regarding the need for schools for clinical instruction in the nature and treatment of mental maladies. Thus Conolly, in 1862, four years before his death, told our predecessors in this Association that schools for psychiatric instruction were the "great want of our profession, and a great impediment to any progress in it. . . . Until you have these schools, you will never be able to command men to take positions of great importance—not such as you would sometimes wish could be found." It was not, however, until 1907 that Maudsley could begin to give practical effect to these ideas implanted so long before. Mott, who had been one of his pupils at University College and who was now Pathologist to the L.C.C. Mental Hospitals, wrote a proposal after visiting Kraepelin's Clinic at Munich, in which he urged the creation of a similar University psychiatric hospital in England which should be devoted to early treatment, research and postgraduate training. This accorded well with Maudsley's views; he got in touch with Mott and made his offer of £30,000 to the London County Council if they would build the hospital, subject to its association with the University of London; this offer, supported by A. J. Balfour and Arthur Rucker, the Principal of the University, was accepted by the London County Council in 1908, but there were delays; the site was not chosen till 1912, nor the building completed till the end of 1915. Before Maudsley died, he had seen the hospital, under Mott's energetic guidance, doing some of the teaching and pioneering work which he wanted, though, of course, it was not till 1923 that it was opened to fulfil all the purposes which

Maudsley had outlined in the article he wrote for the *Archives of Neurology and Psychiatry* in 1909.

It is not for me to examine what effect the existence and activities of the Maudsley Hospital have had upon the advancement of psychiatry, but it is clear that the hospital has been the instrument whereby Maudsley, after his death, continues to be a potent force. If, however, its work were not carried out in his spirit and to further his aims, it would not be Maudsley's inheritor and agent, but his unfaithful steward, writing an ironical footnote on the vanity of human wishes. I have tried, therefore, with such knowledge of Maudsley's views and character as could be got by steeping myself in his writings, to picture him returning to the scene and judging us in the light of his purpose. Two things are certain: that what he saw and disliked he would condemn in good set phrase or scathing epigram; and that everything new or supported by new knowledge would be brought to the bar, not so much of his former opinions on the matter, as of his standards of truth and scientific method, and of his requirement that it should be relevant to the understanding of human nature in health and disease.

I think, when we were planning how to welcome this most worshipful and august of visitors, and thinking how we might fitly conduct our founder to show him to what uses his gift had been turned, we would decide to bring him first to Professor Meyer. Not that neuropathology had been his concern—he was always a clinician who had no laboratory experience or any evident taste for experiment; but because the work done in that department, the outlook and method, the nexus with clinical problems and opportunity, are in the fullest accord with the beliefs he expressed in the *Physiology and Pathology of Mind*, in *Body and Mind*, in *Organic to Human*, and in many essays and addresses. He would even find kindred interests in what may be called the by-ways of Professor Meyer's department; I recall, for example, that he wrote, as long ago as 1867, "It is deserving of remark that the different nervous centres of the body manifest elective affinities for particular poisons. . . . That medicinal substances do display these elective affinities is a proof, at any rate, that there are important though delicate differences in the constitution or composition of the different nervous centres, notwithstanding that we are unable to detect the nature of them. It may be also that there is shadowed out in these different effects of poisons on the nervous system a means which may ultimately be of use in the investigation of the constitution of the latter"—a prescient statement, ensuring his delight on finding how fully Dr. Meyer had turned his prediction into fact.

Where we would wish to take him next I am not so sure; electroencephalography would surely fascinate and delight him, as a fresh disclosure of those delicate traceries and neural activities about which he constantly surmised; or biochemical studies, esoteric to him as to most of us, but in keeping with his faith in the importance for mental disorder of general metabolic and cell chemistry; these might be the most obvious activities to show him next. But if we delayed his entry into the clinical territories, it would probably be at the risk of a sardonic inquiry as to whether we treated any patients nowadays. We would therefore be brief in detaining him while we explained the subtleties

of the relation between the Institute and the Hospital, and the closeness of our connection with other medical schools of the University—a matter always near to his heart—and told him also of the auspicious union effected so lately between his Hospital and that ancient and notable hospital of which his friend Savage was the head, and which had had, long ago in the days of Henry the Seventh, a Thomas Maudsley as its Master and Warden. When in his visit he came to the wards he would find, I think, much being practised which he had advocated and prized—the careful inquiry into history; the regard for physical examination; the concern with individual needs and constitution; the avoidance of liberal sedation; the dislike of rigidity and dogmatism, whether in diagnosis or treatment, theory or practice; the emphasis on the continuity or communality of healthy with morbid; the care for hereditary and eugenic considerations; the social approach to the study and treatment of childhood deviations, of occupational inadequacy, of neurotic deformity and suicidal despair. What he would say about our psychopathology and psychotherapy is a matter for wide conjecture; I think the Jungian doctrines would excite his warmest invective, and the Freudian perhaps his coldest approval—in parts; but seeing that at the hospital we are not all convinced of the rightness of the same theory of psychopathology or the same method of psychotherapy, he would, I imagine, concede that in matters such as these, admitting of legitimate differences of opinion and practice, it is fitting that a University School should allow teachers of proved capacity and experience to put their several standpoints *sine ira et studio*—or at any rate *sine ira*. Then, in the psychological department, he would certainly be pleased to find an animal laboratory and a child development unit, for he had said that the study of the plan of development of mind, as exhibited in animals and in infants, would furnish results of the greatest value and be essential to a true mental science. What he would make of the statistical methods and the study of personality through tests is a hard question, for he liked objective methods and rigorous logic, but had no taste for mathematics. It is significant that in his paper on “The New Psychology” in 1900 he repudiated those psychological studies of animals and of children which used terms without definition and made observations without objectivity, and he extolled the experimental method, declaring that “to express the results in arithmetical numbers or algebraic formulas is a method of demonstration which cannot fail . . . to bring psychology into touch with realities and to put positive meaning into its language.” At the same time he castigated psychophysics for its aridity and neglect of individual differences, and said that though measurements might be “multiplied and accumulated world without end, yet if they remain scattered, incoherent, fragmentary heaps, they will only be monuments of sterile industry—monumental mockeries of knowledge.” So it may be guessed that his judgment of our statistical labours in psychology would be favourable, but reluctantly so, since the bent of his mind was away from ready acceptance of such concepts as the statistical aggregate and uncertain inference, but this may be a hasty conclusion. It is well to remember what Maudsley said at the end of the soundly but rather destructively critical paper which I have just referred to: “I conclude that man as a whole is a larger affair . . . than any single method

of minute inquiry—be it chemical, physical, pathological, microscopical, or psycho-physical—will ever unfold. . . . There is work enough for as many methods of study of mind as are rationally based: have the definite aim of a concrete mental organization to be studied, and work definitely and progressively for it by observation of facts, exclude not one another, but know that in the end they must bring, and, knowing, strive to bring their results into harmony.”

I have said very little about Maudsley's personal life, partly, of course, because the data are meagre, but chiefly because he has plainly shown how he detested to see the trivial and private details of a man's life exposed after his death. Neither have I dwelt upon the themes, few but rather striking, on which the knowledge or the sentiments and experience of our later time would judge him to have been wholly mistaken. Each generation, as Maudsley himself often said, has a common heritage of ideas; each individual mind reflects the thought of its time; and the men of each generation are apt to look kindly but loftily upon the errors and defects of those who preceded them. Few, however, who had become familiar with his thought would feel disposed to condescend to Henry Maudsley, or to dwell, in extenuating advocacy, upon any mistakes into which he fell. He was, I have said it already, a man of incisive and tenacious intellect, a man gifted with unusual foresight, capable of planning and enforcing a great constructive design, such as I believe the inception of the Maudsley Hospital to have been. To his contemporaries at different phases of his long life he seemed other than this; there seem to have been times when they thought him a bitter recluse, given over to mordant nihilism. But they mistook the appearances. It is true, as he once scribbled on a blank page of the *Physiology of Mind*, that he never hated people, but often felt contempt; his contempt, however, was as free from bitterness as his social brusquerie was without malice or any unkindness. I may conclude with recalling the occasion when Maudsley delivered his Presidential Address to this Association: it was in 1871. When he had finished, Clouston took part in the discussion and said: “Dr. Maudsley's address has been one of utter and entire scepticism. He treated three subjects: the prevention of insanity; the sending of patients to asylums; and the treatment by sedatives. And he answered them (thus): Insanity cannot be prevented until we arrive at some future state of human existence in which we shall all live in the light of right reason; patients get much better out of asylums than in them; and do not give sedatives as you will probably poison your patients.” When Maudsley came to reply, he said: “I think Dr. Clouston accurately described my paper as one of scepticism, but in accepting this description of it I would use the word not in an ill sense, as Dr. Clouston might do. I would remind him that scepticism was a very good word before it got an ill meaning: that fundamentally scepticism, and episcopacy, and bishop have the same root; that they all come from the Greek word *σκοπεω* which means to examine, to look to.” To examine to look to—that is what Maudsley always did; he examined the knowledge of his time that had a bearing on psychology and mental disorder, and he looked well to it that out of his consideration of these things should come as much gain of truth, of benefit to the mentally ill, of continuing advancement of psychiatry, as his powers could compass. Such a sceptic we do well to honour.

PRISCOL IN CIRCULATORY DEFICIENCY.

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THE purpose of this article is to illustrate the value, especially over the five colder months, of the peripheral vasodilator, benzyl imidazoline (Priscol, Ciba) in the care of the circulatory disorders of the aged.

The drug has been advertised in the British medical press since January, 1949; but the literature refers to some 10 years. It has consisted mainly of pharmacological studies in animals and man; or has described clinical effects in man over a short period, e.g. as a test prior to surgical measures. An exception is the work of Grimson *et al.* (May, 1948), where periods of trial vary, but in one case extend over five years.

The present article differs from others in describing clinically a group of ten females suffering from circulatory disorders of the feet or legs, and whose previous relevant history was known; and who, during the period of the test, were continuously under survey in an environment whose temperature was known. These conditions were imposed by the fact that the group consisted mainly of typhoid contacts in a mental hospital, but no actual cases or carriers are included. One case, "C," was found accidentally to be excreting for a few days *S. typhi murium*, but she was not showing any signs of dysentery.

It is a well known feature of most chronic conditions that when a patient who was formerly ambulant is compelled by intercurrent conditions to become bedfast even for a few weeks, he loses some of his remaining capacity for co-ordinated and purposeful activity; and this capacity must be laboriously regained in the early days of convalescence. This is a serious enough complication of such illnesses as, for instance, disseminated sclerosis, where the patient may be young and adaptive enough to make the necessary effort. In geriatric and some psychotic cases, however, the situation is aggravated by a tendency to passivity, to give up hobbies, interests, social contacts, and by withdrawing from the environment, to earn the label "demented" or doted. Under these circumstances a combined attack by nurse, physio- and occupational therapist, and social worker, guided by physician or orthopaedic surgeon may be necessary to achieve even limited results. One need not labour the point that considerable effort and vigilance is justified if it will permit such a patient to pursue, unhindered, his few remaining interests without having to take to his bed periodically.

Of increasing importance in this field, owing to an ageing population is a seasonal incidence of circulatory disorders of the feet and legs which is found in a proportion of the patients in the chronic wards of a mental hospital. Among physical conditions, those associated with the names of Raynaud, Buerger and

Bazin spring to mind, but in the present series it was found that arteriosclerosis with myocardial degeneration, and diabetes were numerically more important, among the elderly, especially when associated with depression or inactivity. In the psychotic field are found especially deteriorated or catatonic schizophrenics, usually women.

Whatever the cause, it is common to find cases where the feet in cold weather become cold, swollen, congested and blue, with obviously diminished blood flow, and developing cutaneous sensory loss. These conditions are made worse by tight garters, shrunken stockings and hard leather shoes. When the earlier of these signs appear it is customary to confine the patient to bed with the object of preventing more serious lesions, but in spite of this one may find—

(1) Indolent ulcers of the lower part of the leg or of the pressure points of ankle and heel.

(2) Gangrene of the tips of the toes, which may heal with loss of a little tissue, e.g. nails; or may progress proximally, involving deeper structures.

(3) Several patchy shallow areas of skin death or superficial gangrene on the dorsum of foot or toes. These may be caused by injudicious use of hot water bottles, etc., and take the form of irregular spots of $\frac{1}{2}$ to 3 cm. diameter, where the skin is dry, hard or tough, purplish at first and turning brown. If treated and kept free from infection they show a tendency to heal without breaking down.

(4) Injuries, e.g. falling, due to numbness or muscular inco-ordination.

These, with or without superadded sepsis, were the conditions typical of the group of ten females to be described. Seven of them were over 60 years old, but three other females under 60 were successfully treated with Priscol for similar conditions. They will not be described because their previous histories were not adequately known, and because they were under treatment for a shorter period. On the male side of the hospital was found only one among the over 60's who had an obstinate septic ulcer of the foot with circulatory inadequacy. He responded slowly to Priscol. The total population over 60 was 178 females and 119 males, a ratio of 3 to 2. Since the death rate and the discharge rate of the two sexes were exactly proportional to this ratio; and since the average age at death was the same, 72 years, one might claim that the male and female populations of the hospital over 50 are comparable both physically and mentally. Without suggesting that circulatory disorders of the over 60's attack 6 per cent. of women, but only 1 per cent. of men, there is reasonable evidence of a disparity in their incidence in mental hospital populations. Possible causes of this difference are:

(1) Men dress their bodies and limbs warmer than women, who may be seen with cotton or silk stockings and elbow length dresses even in cold weather.

(2) Men wear boots or shoes which tend to be dearer, and to last longer than women's. They therefore are a better fit for a longer period than women's shoes.

The males in this hospital lived in less overcrowded wards than females, and their opportunities for stimulating outdoor and indoor activities have not been so curtailed by staff shortage.

Survey of Population at Risk, January to April, 1950.

Age-group.	Males.	Females.
60-65	39	48
65-70	35	31
70-	45	99
	—	—
Total	119	178
Discharges	6	9
Died	8	11
Treated	1	10
Percentage	1	6

PHARMACOLOGY OF RELATED COMPOUNDS.

Improvement of the peripheral circulation by interruption of the sympathetic outflow is the aim of various procedures. The pharmacology of this field has advanced during the past 15 years and comprises to some extent the pharmacology of the pentavalent nitrogen atom. One may note, however, that as long ago as 1867 Crum Brown drew attention to the curarizing effects of quaternary ammonium compounds. Generally speaking these compounds owe the intensity of their activity to the number of such ammonium groups in the molecule, e.g. tetraethyl ammonium bromide, with one, curare with presumably two, and Flaxedil (M. & B.) with three; and owe their specificity to the nature of the substituting groups or their position in a homologous series, e.g. in the series of Methonium compounds the pentamethylene produces autonomic block and antagonizes the decamethylene (Davison). The hexamethylene has been used to produce parasympathetic block of gastric secretion and motility (Kay and Smith) and higher members produce skeletal muscular block more marked in the deca- than the octomethylene member (Paton and Zaimis). To digress here for the sake of completeness, it may be mentioned that the simplest of such effective compounds is tetraethyl ammonium bromide (TEAB Boots), which in doses of 0.2 to 0.5 gm. intravenously produces an immediate vasodilation of the foot, with concomitant fall of blood pressure. The patient is usually supine when it is used, to avoid subjective or other symptoms due to this fall in B.P., and the effect on the circulation passes off in a few hours.

A recent addition to the group is the drug Flaxedil (M. & B.), which has three quaternary nitrogen atoms: $C_6H_3(O.CH_2.CH_2.NEt_3.I)_3$. It has a marked curare-like action, no sympathicolytic action, and little parasympathicolytic, in animals; but in man it produces skin flushing and usually a slight rise in blood pressure. For instance, in a patient drowsy with Pentothal who showed relatively little curarising effect, the B.P. before and at 1, 3, 7 mins. after a small dose of 40 mgm. were 134/96, 148/90, 150-142/90, 136/90 mm.

A related substance mentioned here for the sake of its universal interest is nicotine, pyridyl-N-methyl pyrrolidine. It is not a quaternary nitrogen compound, but a di-tertiary one, which is oxidized in the cold by atmospheric

oxygen; and readily forms additive quaternary nitrogen compounds. It is tempting to suppose that a reaction of this nature is a normal stage in its metabolism, for this would account for its well known effect on autonomic ganglia.

The substance mephenesin (Myanesin, B.D.H.) produces a relaxing effect on skeletal muscle; but as an α -substituted glycerol ether it is unrelated chemically or pharmacologically to the nitrogen compounds under consideration.

The pharmacology of Priscol is described as "very complex" by Alquist *et al.*, and consequently side actions are known and even forecast in their paper. They will be described later.

(1) There is, in effective doses, a peripheral arterial dilatation which can be seen; measured by blood-flow meters; and detected by pulse pressure contour studies. This is considered to be partly adrenolytic and partly histamine-like (Hendrix, Grimson), and by Alquist *et al.* to be sympathomimetic-antipressor, similar to certain adrenaline derivatives.

(2) Stimulant action on the heart muscle, with coronary dilatation, a sympathomimetic effect, capable in some dogs and some humans of causing at least a temporary pressor effect in spite of the previous result. Increase in rate of blood flow seems to be invariable.

3. A cholinergic effect on the intestinal musculature and on the cardiovascular system of rabbits.

(4) A histamine effect on the intestine and uterus.

Priscol (tablets of 25 mgm.) was chosen for this investigation, because it has a well marked vasodilator action particularly on the lower limb; because, unlike the other drugs mentioned, it is available in tablet form, convenient for oral administration over a long period, and because it is cheap, costing only about 3d. daily in the small dosage here used, i.e. 3 tablets daily. This small dose was chosen initially with a view to avoiding unforeseeable side-effects, which might occur during a prolonged course of treatment; and as the clinical effects seemed adequate on the whole, there seemed to me no indication for an increase of dose.

It is also available for injection, and is said to be effective when applied topically.

In a group of five specially selected because of the uniformity of their environment over the test period, an attempt was made to determine whether, after three months' treatment, there were any signs of habituation, or whether withdrawal symptoms would be evident. In particular one wanted to know whether the clinical effects were as marked in February as at the beginning of the course, and so the drug was withheld on that date, while observation continued. The Priscol tablets were then given again five days later, and the effect compared with the initial effects.

Ward Temperatures.

The temperature of the ward was noted night and morning, but all the readings need not be given here. Instead, each month has been divided into four "weeks" of seven or eight days, and their morning and night readings averaged separately. The minimum reading for each month is given in degrees F.

Weekly average temperature of ward in month of:

Oct.		Nov.		Dec.		Jan.		Feb.		Mar.	
M.	E.	M.	E.	M.	E.	M.	E.	M.	E.	M.	E.
61	67	51	53	50	54	54	60	54	58	50	58
59	61	50	54	49	53	54	55	52	59	52	59
56	57	50	53	48	55	51	54	55	58	56	60
49	54	52	58	53	58	49	52	52	57	54	59
<i>Minimum:</i>											
48	52	46	48	42	48	44	48	42	48	44	46

It is, of course, regrettable that no information is available about humidity, rate of air-flow, or katathermometer readings, but enough has been shown to indicate that healing processes were not indebted to the environmental temperature.

RESULTS OF TREATMENT.

The effects of treatment are described in notes made from time to time under the headings.

Temperature.

Colour.

Degree of oedema.

Presence or absence of dorsalis pedis pulse.

Duration in seconds of the white mark made by finger pressure.

Blood pressure.

Pulse rate and rate of blood flow to the foot in c.c. per minute.

Progress of lesions.

Side effects.

To describe these in all cases would be tedious, so only three—cases C, I and K—have been given in full. The others have been given in the condensed statement, or under the headings of Signs and Symptoms.

More briefly still it may be said that ten patients who had spent part of the winter '48-'49 in bed on account of poor circulation of the feet, as well as a few of the previous winters, were treated with Priscol. Eight were ambulant, usually wearing slippers throughout the winter '49-'50, and while ambulant their existing lesions healed. One who had a diabetic gangrene was not ambulant, developed wet gangrene and recovered from the consequent mid-thigh amputation. She died in coma. The tenth, case I, was found inadequately clad on two occasions, and was subsequently treated in bed—successfully.

SIGNS AND SYMPTOMS.

Individual signs or symptoms showed the following changes during or after treatment:

Colour.

Ten cases showed cyanosis of feet or toes. One (case C) remained cyanotic; four became pale; three became dusky at times, pale at others.

Two cases, D, K, were pale before and during treatment.

Temperature.

Skin temperature was estimated by two methods :

(a) Touch, the examining hand being " warm," i.e. between 27° and 29° C.

(b) By an ordinary thermometer attached to the skin. The bulb and adjacent skin were covered with a small blob of lubricating jelly which was in turn covered with a layer of fine gutta percha to prevent evaporation.

The latter method was found unsatisfactory as it could not integrate the temperature of a skin area of a whole foot at a time. Consequently, the less accurate but more useful method of touch was relied upon.

It was found that a skin temperature predominantly below 20° C. was judged to be " cold," and one above 27° was considered to be " warm." Between these two temperatures the skin was described " cool." Using these standards, eight out of the ten cases, before treatment, had " cold " feet while in bed ; and they all became " warm " under treatment, though two of them, B and H, were occasionally found to be " cool."

The other two, D and K, were " warm " both before and during treatment.

Oedema.

All cases except E showed oedema before treatment, and none showed any material improvement so long as they remained up. Two cases showed slight increase of oedema, amounting to an increase in circumference of $\frac{1}{2}$ to 1 in. approximately. No attempt was made to control the oedema, by limitation of salt or water intake.

Pulse.

The dorsalis pedis pulse was sought before the patient had got up in the morning, and the feet were usually warm at the time. It was absent bilaterally in all cases before treatment ; during treatment it returned in eight cases. In cases B and E it remained absent in one foot and doubtful in the other.

Blood Pressure.

There is generally a fall in systolic B.P. of 10-50 mm. In three cases the pulse pressure increased by 5 to 10 mm. and in five was unchanged. In one there was a fall in pulse pressure of 15 mm. and in the case A above mentioned the fall was, of course, 27 mm. This is the case which relapsed and needed special attention as described below.

Pulse Rate.

Simultaneous with the fall in B.P. there was a rise in pulse rate which, in round figures, was 65 per minute, rising to 75.

Withdrawal Signs.

In five patients where it was considered safe to do so, the Prisol was stopped for five or more days on February 17, when the ward temperature averaged 54° F. in the mornings and 58° F. in the evenings. All of them showed, during

five days, a progressive return to their original state. The feet became cooler, cyanosis reappeared, and the dorsalis pedis pulse gradually disappeared. All of them showed a rise in blood pressure above its original level. In one case, K, the rise was alarming, and continued for about a month. (See case note.) These withdrawal effects have not been adequately described in the literature. The timing of these withdrawal signs is in line with the findings of Grimson, who, in a few cases, found that treatment need not be continuous, but could be interrupted for a week or more at a time.

In all cases the Priscol was withdrawn finally about the beginning of April, except where stated specifically, when the rising temperature made further treatment unnecessary. The dose was diminished over a week or ten days to zero.

There was in most cases, some deterioration in blood supply ; but no case developed any lesion.

SIDE EFFECTS.

Habituation.

At the end of four months' treatment the drug seemed to be exerting its original effect both on those who had received it continuously ; and also where it was withdrawn for five or more days, and then restarted, the original effects were exactly reproduced as in the first few days of treatment.

Minor Subjective Complaints.

There were no complaints under this heading among the ten cases studied. The reason for this can probably be deduced from their mental notes. None of the three elderly control patients over 60 made any complaint either, but three younger cases who were receiving benefit for Raynaud's disease and chilblains (two cases) each made complaints. One, whose chilblains stopped itching within a few days of treatment, stopped taking the drug because of headaches.

One complained of tingling of legs and chilliness of back and shoulders after the first few doses only.

One (Raynaud's) complained of abdominal discomfort.

Diarrhoea.

Diarrhoea is a recognized side effect, but it was not noticed in the above series. Among the ten were four incontinent patients whose bowel movements were noted at night, as a routine. They showed no increase whatever in frequency of bowel activity during the period of test, compared with the month preceding it.

Leucopenia.

The possibility of leucopenia as a complication of treatment is raised by the mention of a case who, while receiving Priscol (dose ?) received also two daily doses of sod. pentobarbital, 0.1 gm. His W.C.C. fell from 9,000 per c.mm. before Priscol to 3,110 ten days after starting the Priscol and two days after the

Pentobarbital. Two days later it was 5,550 and a month after stopping Priscol had regained its initial value (Grimson *et al.*, 1948).

In this series white cell counts were not done before treatment. In any case they would have been vitiated by the presence of sores or sepsis. White cell counts were, however, carried out on all patients early in April, while still on Priscol. A control group, from the age of 60 to 75, and free from disease, was chosen. In the columns below they are compared, the cases being lettered, and controls numbered. In averaging the case column two figures were omitted: Case C, who was only 35 years, and case I who was known to have pernicious anaemia. This does not actually affect the conclusion, which is that Priscol does not normally diminish the white cell count in doses of 75 mgm. daily.

Cases.		Controls.	
A	7,187	1	5,000
B	6,875	2	5,625
C	10,927	3	5,937
D	5,000	4	5,937
E	8,150	5	3,593
F	3,125	6	5,000
G	3,125	7	7,343
H	6,562	8	6,875
I	3,437	9	5,781
K	6,200	10	5,700
Mean:	5,778		5,679

All counts were carried out by one technician under strictly comparable conditions.

It was still thought possible that a few individuals might exist whose bone marrow activity was already depressed, or were otherwise sensitive to the drug, and who would show a leucopenia after months of treatment, as in cases F, G and I. Hence these cases were counted at 7, 9 and 15 weeks after the Priscol was withdrawn.

In addition, the three controls, 1, 5 and 6, whose W.C.C. were lowest, were given Priscol, 75 mgm. daily for 10 weeks, and their progress noted.

Leucocyte count.						
Case.	On Priscol.	Weeks after Priscol withdrawn.				
		7.	10.	15.		
F . . .	3,125	6,406	5,935	8,437		
G . . .	3,125	3,593	3,125	4,843		
I . . .	3,437	3,125	3,125	7,187		
Controls.	Before Priscol.	Weeks on Priscol.		Weeks after Priscol withdrawn.		
		7.	9.			
1 . . .	5,000	4,531	6,562	3,906		
5 . . .	3,593	5,156	6,562	6,250		
6 . . .	5,000	3,906	5,156	7,500		

These figures show that three controls whose normal W.C.C. was fairly low, showed no significant increase or decrease during nine weeks while receiving Priscol 75 mgm. daily.

On the other hand, three of the cases who had been treated with the drug in doses of 75, 75 and 100 mgm. daily for four months showed a low W.C.C., and a definite tendency to increase towards normal two to four months after withdrawal. Even if one excepts the case I, who was known to need treatment from time to time for pernicious anaemia, the conclusion seems to be that a few cases show, after prolonged dosage, a tendency to a lowering of the white cell count, which, so far as one can tell, is not dangerous or alarming; and which makes a spontaneous recovery, and should not indicate an immediate withdrawal of the drug.

Every white cell count mentioned above was completed with a differential leucocyte count. Nothing of interest was seen, and so they have not been reproduced. For example, the cases F, G and I, at the end of their course of Priscol had the following differential white cell counts, and venous blood leucocyte counts:

Case.	W.C.C.	Venous W.C.C.	Poly- morph.	Lympho- cyte.	Large monos.	Eosin.	Mast.
F	3,125	3,300	71%	28%	0	1%	0
G	3,125	3,467	66%	20%	8%	6%	0
I	3,437	4,375	73%	25%	0	2%	0

These three cases were edentulous and free from oral sepsis; there was no question of agranulocytosis. The high eosinophil count was unexplained.

Notes on Case C, aged 35.

Admitted 17.xii.38 on certificate, as a schizophrenic with paranoid features, lacrymose and violent at times.

Her heart was normal, P.R. 86 p.m., and the general condition was fair. There was no history of tuberculosis.

28.vi.42: She remained apathetic and dull; mute, asocial and suspicious. A small abscess appeared in the right breast, and an ulcer on the left external malleolus. Later, the right ankle ulcerated, and these ulcers did not clear up for several months.

10.xii.43: Dry sores on the ankles. She had a course of E.C.T. and went to work in the laundry.

18.xii.45: Peripheral circulation poor; feet cold and blue.

3.xii.46: Marked cyanosis and oedema of the feet; confined to bed.

11.xii.47: Stands motionless for long periods; ankles very hard and oedematous.

24.xi.48: In bed, and picking at her skin.

12.iv.49: Catatonic, depressed and suspicious; unemployable and reacting badly to treatment with E.C.T. Cyanosis and oedema of the feet, with long-standing ulceration of lower third of the legs, posteriorly. Leucotomy performed.

17.xi.49: In bed, apathetic and idle. The left calf showed an irregular ulcer of about 4 sq. in., while the right ankle showed two smaller areas of about 2 and 1 sq. in. The floors of these ulcers were dry, dark in colour and showed no signs of healing. (Pulseless.) B.P. 160/110 mm. Received Priscol, 25 mgm. *t.i.d.*

17.xii.50: In bed; feet cool, pale, free from oedema, but still pulseless. Ulcers were scabbed over, and diminished to half the above measurements. Priscol was increased to 100 mgm. daily, and she was allowed up, wearing long woollen stockings, without garters.

12.iv.50: Ambulant; ulcers soundly healed, but with the skin thin and glossy over their sites. There was brawny oedema of both legs, and B.P. 144/100 mm. Cyanotic.

Condensed Statement of Results.

Case.	Age.	Former lesions ; and condition in November, 1949.	Duration (years).	Result of treatment, 31.iii.50.	Mental state.
A	68	Varicose ulceration, with scarring and much loss of tissue	10	Remained well ; ambulant	Paraphrenia.
B	48	Healed phthisis ; scarring and oedema <i>Ulcer right calf, ? Bazin</i>	20 $\frac{1}{2}$	Healed ambulant	Ad. 1930 ; cert. schizophrenia
C	35	Bazin ; <i>bedfast with spreading ulcers of both legs</i>	7	Ditto	Leucotomized ; catatonic schizophrenia ; apathetic
D	52	Extensive scarring ; obese with four large septic ulcers	5	Healed ; ambulant later	Depressed ; toxic confusion ; ad. 1949
E	78	Unstable diabetic <i>Gangrene of fourth left toe partly healed</i>	? 1	Moist ; amputated ; healed	Organic dement ; died in coma three months later
F	75	Scars of sores and shallow ulcers. <i>Blood blisters</i>	4 $\frac{1}{4}$	Healed ; ambulant	Feeble-minded deaf mute
G	64	Lymphangitis, sepsis and oedema <i>Cellulitis</i>	9 $\frac{1}{2}$	Ditto	Ad. 1930 ; cert. epileptic
H	73	Oedema both feet <i>Ulceration both feet</i>	2 1	„	Ad. 1908 ; chronic mania
I	61	Loss, by gangrene, of tips and nail of 6 toes ; brown stains of skin-gangrene, healed <i>Recent spots of skin death</i>	6	„	Pernicious anaemia ; dementia
K	75	Gangrene toes and ulcerating sores Fracture femur <i>Incipient gangrene</i>	30 3 $\frac{1}{4}$	„	“ Religious mania ” ; dement

Lesions indicated in italics actually existed and demanded treatment during the month of November, 1949.

Extract from Notes on Case I.

14.xi.49 : Bedfast, her feet cold, cyanosed and pulseless ; slightly oedematous, with numerous small areas of skin death scattered over the dorsum of feet and toes, some recent, others healing, but all dry and hard.

The finger-nails were normal, but all the toe-nails were absent or atrophic, and the tips of seven toes lost as a result of attacks of gangrene during the last six years.

She was put to bed and given Prisol, 25 mgm twice daily. By the next day her feet were warm and pale, both dorsalis pedis pulses being palpable. B.P. 150/80 mm. P.R. 60 p.m.

24.xi.49 : Her feet were found to be cool, so the dose was increased to 25 mgm. *t.i.d.*

29.xi.49 : Feet were warm, pink, and all the skin lesions were healing. There was no apparent oedema, the circumferences of ankle and forefoot* being $15\frac{1}{2}$ in. and $15\frac{1}{4}$ in. on both limbs. Both pulses were palpable.

30.xi.49 : Allowed up.

* The sum of the circumferences of the forefoot behind the first metatarso-phalangeal joint, and of the ankle above the malleoli, on each foot.

11.i.50: Her feet were cold, dusky, pulseless and oedematous, the circumferences being now $16\frac{1}{2}$ in. on both legs. The blood pressure had fallen to 106/70 mm., but the Priscol was now given 6-hourly and she remained ambulant.

12.i.50: Found seated motionless and idle as usual, but quite inadequately clad, with elbow-length frock, cotton stockings, garters, when the ward temperature was 52° F. All the peripheral skin areas, face, neck, arms, hands and thighs were cool or cold. There were several fresh areas of skin death, brownish and papery, with some blister formation, on the dorsum of the feet and most of the toes.

14.i.50: Ambulant, with particular attention to dress, e.g. woollen stockings to mid-thigh, held up without garters, and warmer dress—cardigan. General condition no worse.

15.i.50: The skin was found broken on dorsum of 3rd right toe and behind both heels, probably due to new leather shoes worn inadvertently instead of her own slippers of felt. Her feet were cool, cyanosed and oedematous, $16\frac{1}{2}$ in., $16\frac{1}{2}$ in., and fingermarking for five seconds. B.P. 130/85 mm. P.R. 72 p.m. She was kept in bed, where her feet became warm and dusky, fingermarking for three seconds, but still pulseless.

19.ii.50: Her feet were healing satisfactorily, warm and dusky, both pulses having returned faintly. They were slightly oedematous, measuring 15 in., $15\frac{3}{4}$ in., fingermarking for five seconds. The B.P. had risen to 148/78 mm. P.R. 64 p.m.

20.iii.50: The feet were satisfactory, warm, pink, without oedema and healed. The B.P. showed a continued tendency to rise, 160/80 mm. P.R. 78 p.m.

3.iv.50: Blood examination showed a slight symptomless leucopenia, R.B.C. 3,768,000 per c.mm. Hb. 90 per cent., C.I. 1.2, with slight anisocytosis. (Progress of W.B.C. elsewhere.)

Notes on Case K, aged 75.

Admitted to this hospital in 1895 as a case of "dementia" resulting from "religious mania" she is now amnesic, confused, idle, unable to care for her daily needs and unable to converse. She has a long history of peripheral circulatory disorders, chiefly affecting the feet.

25.iv.10: Vasomotor paresis; cyanosed extremities with small ulcerating sores of the feet.

10.i.11: Confined to bed; small sores on the feet.

11.i.12: Confined to bed; small sores on the feet.

31.iii.13: Tips of second left and third right toes gangrenous. Healed slowly with some loss of tissue. In bed part of every winter.

1.ix.33: Feet blue and oedematous.

14.ii.46: Fracture of neck of left femur, with ultimate recovery.

21.i.49: Confined to bed (till April, 1949).

5.ix.49: Sore on right shin. B.P. 140/93 mm.

27.xi.49: Third left toe shows early gangrene. The feet are warm and pink, but swollen to 9 in. round the instep and pulseless. She was given Priscol, 25 mgm. *t.i.d.*, and her progress was as follows:

27.xii.49: The feet were warm and pink, but oedematous, the sums of the circumferences of the forefoot and ankle being 17 in. and $17\frac{1}{2}$ in. Fingermarks lasted for four seconds. The pulses were palpable, B.P. 132/100 mm. and P.R. 65 p.m.

3.i.50: Third left toe healed; allowed up.

1.ii.50: Feet were warm and pink, fingermarks lasting two and 4 seconds, but the oedema had slightly increased to $17\frac{1}{2}$ in. and 18 in. The pulses were present, the B.P. 130/90 mm., P.R. 60 p.m.

5.ii.50: Volume of blood flow through foot (left) was 15 c.c. per minute. (See below.)

17.ii.50: Priscol was stopped till 20.iii.50. Confined to bed.

18.ii.50: Feet were cool, dusky, fingermarking for five and eight seconds, but otherwise unchanged. The blood pressure was 140/90 mm. and P.R. was 70 p.m.

19.ii.50: Feet unchanged, but B.P. now 150/105 mm. and P.R. 48 p.m.

23.ii.50: The oedema diminished to 17 in., 17 in., and fingermarks lasted only two seconds. The feet were pulseless. The systolic pressure varied between 190 and 212 mm., diastolic remained at 105 mm. P.R. 60 p.m. The morning urine contained 1.95 per cent. urea, and a faint trace of albumen. The blood urea was

45 mgm. per cent. Rate of blood flow through the left foot was now estimated at 2 c.c. per minute.

27.ii.50 : Feet remained as before, the oedema diminishing to $16\frac{1}{4}$ in. and $16\frac{1}{2}$ in., and the systolic pressure varying between 185 and 170 mm., while the diastolic was 80 mm. P.R. was 52 p.m.

20.iii.50 : Feet as before and blood pressure was 142/75 mm. P.R. 58 p.m. Prisol restarted and patient allowed up.

31.iii.50 : Feet warm, pink, fingermarking for three seconds. Both pulses were present and B.P. 132/95 mm. P.R. 65 p.m. Rate of blood flow estimated at 12 c.c. per minute.

Rate of blood flow was estimated by a plethysmograph method. A bivalve transparent plastic case, made gastight with adhesive plastic strapping was applied to the foot and ankle. It fitted fairly snugly round the ankle and was lightly packed with cotton wool and vaseline at the ankle to minimize accidental movement. Air displaced from it drove a small plug of water along a horizontal glass tube for measured distances. The venous return was occluded at zero seconds as usual by suddenly inflating a sphygmomanometer to 30 mm. below diastolic pressure (Lovatt Evans, 1947, and Barcroft and Walker, 1949). The estimated rate of blood flow is probably less than the actual rate, but the following figures have a comparative value.

Rate of Blood Flow.

Date.	Lapse of time, secs. after occlusion.				Estimated rate of flow c.c. per min.)
	5.	10.	20.	30.	
5.ii.50	Prisol . Vol. displ. (c.c.) .	1.10 .	2.50 .	4.80 .	—
	75 mgm. daily . Rate of flow (c.c.) .	13.2 .	15.0 .	14.4 .	15
26.iii.50	Off Prisol . Vol. displ. (c.c.) .	— .	.25 .	.70 .	1.0 .
	9 days . Rate of flow (c.c.) .	— .	1.5 .	2.1 .	2.0 .
31.iii.50	Prisol . Vol. displ. (c.c.) .	.90 .	1.9 .	3.7 .	—
	75 mgm. for 5 days . Rate of flow (c.c.) .	10.8 .	11.6 .	11.1 .	12

CONCLUSIONS.

Prisol is a valuable and safe drug in the care of the circulatory disorders of the elderly. It may enable them to remain symptom-free during cold weather without becoming bedfast.

In ambulant cases it does not help oedema caused by stasis. In one elderly diabetic it may have precipitated wet gangrene, where dry gangrene existed.

Side effects in elderly people are negligible where the dose is 100 mgm. daily or less. The drug should be withdrawn gradually.

I should like to thank Dr. Lorrigan, of Ciba Laboratories, for his helpful advice and criticism ; and Dr. McGregor, of Saxondale Hospital, for his interest in the work. I am very grateful to Mr. Hubbard for the blood counts.

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CHILDHOOD SCHIZOPHRENIA AND MENTAL DEFICIENCY.

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IN 1933 Potter expressed the opinion that a careful psychiatric study of patients in institutions for mental defectives "might demonstrate that schizophrenia in children is not as rare as is now generally believed." Similarly in 1938 O. Lay wrote: "It is possible that many cases exist in institutions for the feeble-minded, in which the disorders have been assumed to have existed from birth, and that a close examination would reveal that in the earliest years the patient's development was normal."

In the same year Despert made some interesting suggestions as to how these children reach their final destination. "In conclusion, we believe that schizophrenia in children is not so rare as formerly believed. As pointed out by Potter, an analysis of the anamnestic data of some of the children in the institutions for the feeble-minded would demonstrate this. It is possible that these patients could retain a certain degree of adaptability to their environment after the initial loss of contact, and even for some time continue their attendance at school. It is possible that they are brought to the attention of the qualified psychiatrist only at the stage in which they appear to be feeble-minded rather than psychotic."

Although many workers in mental defective institutions have investigated the relationship of psychosis and mental deficiency, the mental defect has usually been regarded as primary and the psychosis as superimposed, without sufficient evidence being reported in the form of anamnesis and mental test results to justify the assumption.

The present investigation has been restricted to the study of patients who, without original intellectual defect, have developed schizophrenia during childhood and been ultimately disposed of to a mental defective institution. Such patients have, in most cases, suffered from schizophrenia for some years. This fact brings some advantage to the investigator. Firstly, it facilitates diagnosis, for since Homburger it has been accepted by most authorities that childhood schizophrenia cannot be diagnosed on clinical grounds alone, but only with a knowledge of the course and outcome of the disease. Secondly, it provides interesting information of what happens to these patients when they grow up.

The limitations of the present study should be made clear. Firstly, it is confined to patients ultimately disposed of in a particular way, and, therefore, does not provide a true cross-section of those afflicted. Secondly, the method of approach has been to single out patients presenting the clinical picture of schizophrenia, and then to make further inquiries. Kraepelin, and

a few authors subsequently, have noted that a patient developing schizophrenia in childhood may appear later to be an imbecile indistinguishable from imbeciles of different origin, on account of long intervals of freedom from process symptoms. Such cases are, therefore, not included in this study, as the author has not yet made a systematic investigation of case-histories. Finally, except in a few outstanding cases, the thorny problem of the differential diagnosis of idiocy has been avoided, and the many patients of that grade displaying symptoms that might be regarded as schizophrenic have been largely excluded. The findings are, therefore, biased in respect of both the terminal mental level at which these patients function, and of their frequency in the institution.

Sixteen patients appear to be cases of childhood schizophrenia without previous mental defect, either on the evidence of the history, or because mental tests demonstrate that the intelligence level is still within normal limits. Five of these have been tested on the Wechsler-Bellevue scale, and their Intelligence Quotients vary from 80 to 100. A sixth patient, only here for a few months, was probably of the same order of intelligence. The others could not be tested, but one of them can read and write quite well. Of these 16, 12 are males and 4 females, a sex ratio which accords with published findings for childhood schizophrenia. In addition to these cases there are 6 of whom it is impossible to be certain that there was no primary mental defect, or that schizophrenia began in childhood. This makes 22 cases in all. The two groups are treated separately. As the account given below reveals, the information available is far from adequate and its completeness varies from case to case. Some of it has been obtained by interview, some by correspondence, and a little from statutory documents.

A selection of characteristic cases is described in detail, and the findings of the whole series analysed. Special attention has been paid to the elucidation of the following questions :

- (1) Relationship of age of onset to resulting mental grade and degree of dementia.
- (2) Relationship of intensity of disease process to form of symptoms.
- (3) Relationship of age of onset to form of symptoms.

Attention has been paid to distinguishing between mental grade and dementia, which may easily be confused. The following criteria have been used :

MENTAL GRADE.

This was judged, where possible, by results of mental tests ; where not, by ability to read and write and carry on a conversation. Dementia may interfere with speech, but often a demented patient will be heard talking to himself, or will utter some surprise remark. In several ways the occasional intrusion of intelligent behaviour through the interstices of the psychotic pattern reveals an unexpected capacity.

DEMENTIA.

In a high-grade patient, dementia is considered to be absent if the patient conforms to basic social demands, such as clean toilet habits, washing, dressing and feeding, answering when spoken to and giving an account of

himself in conversation. Its presence is recognized, apart from failure to adapt in above-mentioned respects, by irrelevant, incoherent or mumbling answers, with wandering of attention, when addressed. More severe dementia is shown by mutism, giggling, echolalia or moving away when approached, showing complete absence of any attempt to conform to the important social requirement of maintaining contact with fellow men. Incontinence and refusal to wash and dress are evidence of extreme dementia.

It is clear that these criteria are of progressively diminishing applicability as the slope of mental capacity is descended, for on the plane of idiocy social adaptation is practically absent. At this level the presence of schizophrenia is chiefly recognizable by positive findings, such as motility disorder and positive avoidance of all social contact. As already mentioned, the idiots have not been subjected to a thorough study except in a few outstanding cases. Such a study was made by Earl (1934.) We have the impression, however, that different clinicians would differ in their opinions in many cases. A history of deterioration in idiots is an insufficient and uncertain criterion, not only because there is no such history in some cases of childhood schizophrenia of very early onset (Benda), but also because a number of idiots deteriorate as a result of progressive organic changes as in epiloia, for instance, and cerebral dysrhythmia (Kennedy and Hill).

In addition to the diagnostic problem of determining the absence of prior mental defect in a child afflicted with schizophrenia and of distinguishing between dementia and low mental capacity, there is that of deciding where to draw the line between schizophrenia and schizoid psychopathy. This we treat as an arbitrary matter. There is very likely a continuous variation in respect of "schizophrenicity" from the normal to the frankly psychotic. One or two cases described in this paper might be regarded by others as schizoid psychopaths.

A Selection of Cases in which Absence of Original Defect Appears to be Certain.

CASE I.—N. G—, male, aged 21 years.

The third of three children. Mother 31 years old at the time of his birth. Full term; normal labour. Breast-fed for a short time. While still an infant was adopted by the mother's sister and brought up in Wales. Not seen again by the mother until he was 14 years old. The reason for this was that the mother had two other children, and had to go out to work. She was also ill-treated by her husband, who struck her several times while she was pregnant.

According to the aunt, between the ages of two and four years he developed peculiarities which were not those of a normal child. He was very temperamental and dogmatic in his demands for anything he desired. "As you will agree, a normal child could be consoled and talked out of wanting something, but this was not so in the case of N. G—. He always gave vent to his feelings by a sort of hysteria. His mind could not understand the meaning of a refusal in any form of the things he wanted." He showed normal affection to his aunt and her daughter, but was abnormal in his relations to other children, refusing to mix with them or to play with them. He was very destructive when playing with small toys, but a tricycle afforded him much pleasure. At an early age he was fond of such games as ludo and snakes and ladders.

He learnt to walk and talk at the expected times, and learnt to read unusually early. Before the age of 5 years he could read children's books, and preferred doing so to anything else. By the age of 7 years his favourite literature was the

Children's Encyclopaedia. At about this time he developed a keen interest in maps, and soon developed an especial enthusiasm for the geography of the Isle of Man (which he still has). This became (and remains) something of an obsession with him, and he believes his name is an Isle-of-Man name. Before the age of 14 years he had developed an extensive and detailed knowledge of geography, scripture, astrology and biology. At school he was about average, being advanced in general knowledge, fair at French, but definitely backward in mathematics. It was noted in the school report that he was no good at doing anything with his hands.

He began to masturbate at the age of 3 years, and has remained strongly addicted to it ever since.

Between the ages of 10 and 12 years he developed a strong tendency to wander. He used to wander off at intervals without any indication of where he was going, and "when questioned why he had been somewhere," he seemed undisturbed at the trouble he had caused.

At the age of 14 years he returned to his mother, who had divorced her husband and married a second time. He was very upset at this as he had believed the aunt to be his mother. He became incontinent for a time, and his tendency to wander and stay away increased. He underwent some improvement, but was never employable and easily became excited. Spent much of his time reading books and concerning himself with abstruse matters. Pondered deeply upon the problem of what year preceded A.D. 1: was it 0 or not?

Was admitted to this institution at the age of 18 years, and since has undergone a certain amount of deterioration.

Present condition.—Clean in habits; washes and dresses himself. Is able to read and write. Does a little ward work if supervised. Sits about most of the time reading. Talks to other patients sometimes and occasionally gets excited and shouts. Can carry on a conversation and give quite a good account of himself, but will soon bring the conversation round to the content of his ruminations, such as the Isle of Man. When being tested, interrupted the procedure from time to time with such talk as the following: "You a psychologist aren't you, doctor? That used to be the study of the soul, but now it is the mind, isn't it? Do you think it is possible to know the soul, doctor?" And so on. His knowledge of certain subjects, such as geography, is encyclopaedic, but although he can answer many difficult questions, he is often ignorant of simple facts, even in his pet subjects. There is no sense of proportion in his learning, and in his mind the intricate byways of human knowledge have the same status as the broad highways, and they are traversed indiscriminately. (He knows the length of the longest river in China, but thinks the height of the average English woman is six and a half feet.) The reason for this peculiarity, of course, is that he learns without any consideration of practical needs. He studies no subject systematically with a view to mastering its principles, but wanders through it as if it were a maze. It is partly the expression of an obsessive ruminative tendency.

He has no delusions or hallucinations and no psychomotor symptoms. He shows no affection and, according to his step-father, avoids allowing anyone "to get at him" by making irrelevant remarks. Intelligence quotient on the Wechsler Bellevue full scale is 85, being 104 on the verbal and 67 on the performance.

Progress.—Slight deterioration in behaviour since admission, but has developed no new symptoms.

Family history.—The father evidently suffered from paranoid symptoms. He was so suspicious and jealous that he would accuse his wife if she merely answered the door to a tradesman. He eventually came to believe that the patient was not his child. The mother divorced him while the patient was in Wales. The mother and other two children appear to be normal and quite intelligent.

Diagnosis.—Childhood schizophrenia of simplex type. Dementia very slight and mental grade in the dull and backward group, or just within normal limits.

CASE 2.—J. H—, male, aged 21 years.

An only child, and the mother was 28 at the time of his birth. Full term baby of 9½ lb. Labour was normal and lasted 12 hours, but the mother was very ill with puerperal infection and it was six months before she looked after the child herself. The child was bottle-fed, and feeding was supervised by the family doctor. Thrived badly and was taken to a specialist at the age of three months. Fuller diet pre-

scribed and nurse engaged. According to the mother "the nurse was a bully and would not let me interfere." The child continued to scream for a few weeks, but then began to improve. At six months the nurse left and the child was looked after by mother with help of her sister. Weaned at 9 months. Walked at 11 months, and began to talk even before that. Bladder and bowel control established fairly early without especially coercive training. He appeared to be quite quick, and played normally with other children.

Mother states that he was never affectionate or demonstrative to anyone. "He never seemed to be mine." He preferred the aunt, but even with her he was distant. Father was in the army and often abroad.

At the age of 3 years he developed the peculiarity of refusing to stand or walk on mats, and of screaming if he ever did so. A doctor managed to cure him of this in one session.

Between the ages of 4 and 6 he showed a dislike of being handled, and refused help when going to the lavatory or dressing.

At the age of 6 years his behaviour deteriorated. He became disobedient and irresponsible. He would run into the middle of the road, he swore, truanted, showed a marked dislike of girls, and attacked smaller children. He used to behave in a manner which would embarrass his mother in public. He used to behave in a silly way on purpose. For instance, he would point to a horse and call it a cow.

At the age of 8 years he was seen by Dr. Cyril Burt, who recommended a boarding school to teach him independence. He did not fit in there. He refused to play games or with other children. He used to play practical jokes, and there is some evidence of homosexual interests. He did not appear to be learning anything, and did not do what he was told in class. It was thought that he could not read, but quite unexpectedly and out of turn he once stood up and read a paragraph perfectly. He disliked school, and there were stormy scenes at home at the end of the holidays. At the age of 10 years he was seen again by Dr. Burt who was disappointed at the lack of progress. At that time the mother went to India for two years following the advice of the headmaster, who thought holidays unsettled the boy. On her return she took him to Broadstairs, where he was unmanageable and beyond control.

Two other schools were tried, but at both he was difficult and often destructive. On holiday, he would be unmanageable. On the bus he would insist on taking a train, and vice-versa. Once insisted on walking five miles home, and on one occasion attempted to push a girl under a bus.

He was sent to Camberwell House, where six months' E.C.T. proved ineffectual. Was there for five years, and then transferred to Middlesex Colony.

Present condition.—Clean in habits. Washes and dresses himself. Is able to read and write. Unemployable. Sits about in the ward either doing nothing or reading in a very monotonous voice to a patient with Fröhlich's syndrome, in whom he seems to take an interest. Also writes letters for some other patients who cannot write.

Although his mother can carry on a conversation with him sometimes and he talks to some patients, it has never been possible for a member of the medical staff to converse with him. He answers questions in monosyllables or in a few words, sometimes to the point, sometimes not. Occasionally shows echolalia. No motor symptoms, except for a somewhat rigid posture and gait. No evidence of hallucinations or delusions.

Lacking in affective expression, and when answering questions does so in a foolish way, with a monotonous drawling voice and an inane grin. One is never sure if he is joking or not. Occasionally impulsive, but on the whole is quiet and shows no signs of aggressiveness. Once went home on leave, but became violent and unmanageable when the time came for his return to the institution.

Progress.—Has shown very little change during five years here, or previously for five years at Camberwell House, but the general impression is that he has become somewhat quieter.

Family history.—No history of mental illness. Mother is Scotch, quite well educated and intelligent. Does not appear to be nervous and is not demonstrative.

Diagnosis.—Childhood schizophrenia of hebephrenic type. Onset at 3 or 4 years of age. Slight deterioration during last ten years. Dementia moderate. Mental grade difficult to assess, but probably falls in the feeble-minded group.

CASE 3.—G. C—, male, aged 29 years.

No birth history available. Walked and talked at the expected ages. "He did not appear backward at all when young, in fact he was a very bright child and inquisitive." He was always highly strung. He was very fond of animals, dogs in particular, until he was about six years old, when he was frightened by a large dog. Since that time he has been terrified of them.

From an early age, although he was an affectionate child, he could be very much the reverse, and his moods would change quickly. For a time he would get on quite well with his two sisters, then he would change suddenly, become quarrelsome, and hit them.

He was at an ordinary school from 6 to 11 years, and was then transferred to a special school. At about 11–12 years it was noticeable that he would not mix with people for long without being quarrelsome and offensive for no apparent reason. For this reason the parents avoided bringing him into contact with strangers as much as possible. When 13 or 14 years old he began grimacing and talking to himself at times.

As he became older the quarrelsome moods increased in frequency, duration and severity, often with violence, and he would have to be humoured and coaxed quite a lot before he would be calmed. His mother was the only one who could do anything with him. In between these moods he was quite happy and sociable, and liked reading *Comic Cuts* and cutting articles out of the papers.

The tendency to grimace and talk to himself increased, and it became more difficult to hold his attention. By about the age of 19 he could not keep his mind on anything for more than a few seconds, his attention and his gaze wandering restlessly. No further information available.

Present condition.—Clean in habits. Impossible to hold a conversation with him. Quite unemployable. He talks incoherently in short and usually incomprehensible words or phrases, turning his head this way and that, like a bird, as he does so. His movements are altogether quick and nervous. Grins frequently, and sometimes emits a hollow laugh devoid of affective content. Some nervous movements of the fingers, but no catatonic movements or postures. Impossible to assess whether hallucinations and delusions are present. Not subject to impulsive outbursts.

Family history.—Parents were normal. Sisters normal. No known case of mental abnormality in the family.

Progress.—Some dementia since admission. Does not now appear to be undergoing any change.

Diagnosis.—Childhood schizophrenia with onset at about 6 years, with slow, steady advance, leading to dementia of considerable degree. Mental grade probably feeble-minded, judging from the history. Was evidently able to read and write.

These three cases form an interesting series demonstrating that knowledge of the age of onset gives no indication of what the outcome will be. The case with latest onset shows the most severe dementia.

CASE 4.—S. S—, male, aged 20 years.

Normal birth and delivery. Breast fed for 11 months. Walked at 14 months, and talked a little before that. Clean in habits at 18 months. This was the first child, and as the mother had previously had a miscarriage, she was terrified of losing him. She never left the house for some time and would not leave him for a moment. He was the most affectionate of the three children, and also a particularly good baby, the quietest of the three. He was less active also, and did not run about as much as the others.

At the age of 22 months the mother was taken to a maternity hospital for the birth of her next child. She was taken in a taxi by her husband. The patient also went, and after the mother had been left at the hospital the patient was taken on to stay with a relative. After the mother's return the family intended to go somewhere by car, but the patient screamed and would not do so. It was three months before he could be persuaded to enter a car.

By the time he was $3\frac{1}{2}$ years old the younger sister was as advanced as he was, and the mother realized that there must be something wrong. She had noticed already that he always "took the line of least resistance," and that he was lazy and solitary in type. He was seen by a doctor, who said that he was backward.

He used to play with toys. He liked building with bricks, and was particularly

interested in floating things on water. He was gentle, never breaking a toy, and did not like mechanical things, or "anything that had to be wound up."

He went to school at the age of 6 years, but made poor progress. He used to "act silly" to make the boys laugh, and refused to attempt any writing, although he would do sums in his head. He was transferred to a special school at 11 years. After a few years there he was transferred to this institution. While at the special school the youngest son was born, of whom the patient was very jealous. He used to frighten him and overturn his chair. His condition before admission was such that he could be made to do a little shopping, and to help with washing up, but most of the time he was idle and sitting doing nothing.

Present condition.—Clean in habits. Slight reading ability, but cannot write. Unemployable. Will not converse with a member of the staff, but will answer simple questions sensibly. Occasionally converses with a patient; will converse with his parents. Usually sits about apathetic, silent and idle. Occasionally averts gaze and shields face when spoken to. Has become bolder recently and is aggressive sometimes, striking out, kicking, and occasionally shouting for no apparent reason. He grins and giggles and slaps himself with his left hand. Needs supervision as regards washing and getting up in the morning. No delusions or hallucinations.

Family history.—Father is a builder and decorator and appears to be normal. The father's sister at the age of 16 years had to be taken to work and brought back because she was nervous of travelling alone. The mother is shy, and also tends to avert her gaze and shield her face during conversation. One sister of the mother has asthma. Two brothers and two sisters are normal. The patient's brother and sister are normal. The sister has matriculated.

Progress.—There has been a moderate degree of deterioration since admission five years ago.

Diagnosis.—Childhood schizophrenia. Age of onset indefinite, but before school age. Considerable dementia. Probably falls within the feeble-minded group.

CASE 5.—A. N—, female, aged 21 years.

Available information scanty. Normal birth. Walked and talked at the expected ages. At 18 months used to take her doll's pram out and go for walks with her mother, who was surprised at the distance she could walk. As a child she was always clean and tidy, and used to fold her clothes neatly. She used to play with dolls and toys like other children.

She never mixed much, did not make friends, and was always shy. She was at an ordinary school until the age of 10 years, when a special school was advised on account of backwardness. War broke out at that time and she was evacuated for two years. On her return she was increasingly shy, especially of men. She did not then get on at all with her two brothers, and used to lock herself in her room at night. For a time she thought people were talking about her when travelling by train or bus. Was admitted here at the age of 18 years.

Present condition.—An attractive, delicately built and fine-featured girl. Clean in habits and tidy. Practically unemployable. Blushes on the slightest provocation. For some periods she is practically mute and stands about by herself; at others she is more lively, with quick excitable movements and nervous speech. It is not possible to carry on much of a conversation with her on account of extreme nervousness, nearly every sentence being interrupted by giggles. It was possible to perform a mental test, although the result probably is not quite valid. Wechsler Bellevue Full Scale showed an I.Q. of 49, verbal and performance items being about the same. However, she reads fluently, and it is most unusual for a person with so low an Intelligence Quotient to do so.

No evidence of delusions or hallucinations and no catatonic symptoms. No particular affection for anyone.

Family history.—Father not living. There are two brothers, one older and one younger than the patient, who are normal. Mother is normal.

Progress.—Slight deterioration.

Diagnosis.—Childhood schizophrenia. Age of onset uncertain. No deterioration. Feeble-minded.

CASE 6.—V. W—, male, aged 21 years.

Eldest of three boys. Walked and talked at the expected ages. Appeared to the parents to be normal until about the age of 3 years, when they realized there must

be something wrong because it was impossible to carry on a conversation with him. He was taken to two different specialists during the next 12 months and was diagnosed as being a mental defective. At the age of 3 years he had an exceptional memory for words and lines, but would not converse. He just repeated anything that was said to him. He was fond of music from an early age and used to play with toys, but preferred to play by himself, and would not do so with his brothers or any other children.

As he became older he became more and more withdrawn and inaccessible, and spent much of the day running about the house and garden humming or talking to himself, and resented being interrupted except at meal times. He became more of a problem as he approached puberty and began to masturbate frequently. He was admitted to this institution at the age of 16 years.

Present condition.—Clean in habits. Dresses himself. Unemployable. Unable to read or write (never attended school). He is of tall, slim build, markedly leptosomatic. He stands about in the ward, often with both hands clapped to his ears. Possibly hallucinated. Is usually quiet. It is not possible to converse with him, and he displays pronounced echolalia. He shows slight catatonic features, and his posture and gait are somewhat rigid and stereotyped. Voice monotonous, and his whole behaviour is entirely lacking in affective expression. His parents used to bring him fruit and cakes, but directly he had eaten them he would say "Mummy go," or "Daddy go," and they now find it too distressing to visit him.

Family history.—Parents of normal intelligence. The father runs a business, and the mother is now a complete invalid with disseminated sclerosis. The brothers are normal.

Progress.—He has become quieter since admission. No other change.

Diagnosis.—Childhood schizophrenia with onset at or before 3 years. Considerable dementia and of feeble-minded grade.

CASE 7.—H. J. C.—, male, aged 20 years.

Normal pregnancy and labour. Mother 30 years of age at the time; 9 lb. baby. Breast-fed for 9 months. First words at 12 months, and able to walk alone at 14 months. Bowel and bladder control at about 18 months. He is the fifth of eight children, and of them all he was the most affectionate towards mother. From the start he was a shy child and did not like mixing with others, but he used to play with his brothers and sisters quite normally. At the age of 3 years, about the time a younger sister was born, he started wandering away from home and began to be a little more withdrawn. At 4-5 years he became increasingly restless, especially at night. Went to school at the age of 5, from which he frequently truanted. At 7 he was estimated to be 2 years educationally backward.

At 8 years he was evacuated and returned to his parents at the age of 13, at which time the father was away in the army. He took no interest in his brothers and sisters at this time and showed general lack of interest. When the father returned the next year, although he recognized him, he denied that it was his father and at times behaved violently towards him. By this time both parents felt they had lost contact with him, and sometimes he sat in the garden day and night making faces and talking to himself. After some months he improved, and it became possible to converse with him. This improvement lasted some months, and then he deteriorated again. He was eventually disposed of to this institution, where he has now been for several years.

On admission.—It was possible to converse with him, but speech showed some dilapidation and was occasionally incoherent. He was clean in habits and able to wash and dress. He was shy and often blushed when addressed. He sometimes successfully achieved a semblance of sociability by adopting a somewhat forced and unconvincing hilarity of manner. On other days he was dreamy and difficult to converse with. He was able to work in the gardens for a time, but after a few months he passed into a catatonic stupor. From this he emerged after a month but was never again employable. He passed into a stupor again later and emerged from this after a course of E.C.T., but remained more demented than previously. He is now idle, apathetic and unemployable. He obeys simple commands, and answers some questions in a very faint voice. He feeds himself, but needs supervision in respect of washing and getting up in the morning. He now presents as a case of catatonic schizophrenia differing in no important respects from that which occurs for the first time in adult life. He does not show characteristic catatonic

postures, but grimaces sometimes, and from time to time hits a patient for no apparent reason.

Family history.—Parents and all siblings normal. No known relative with schizophrenia or mental deficiency.

Diagnosis.—Childhood schizophrenia with onset probably at about 3 years, and considerable dementia. Feeble-minded grade.

CASE 8.—F. S—, male, aged 46 years.

Information scanty, but original defect excluded because the Intelligence Quotient is now 97. He learnt to walk and talk at the expected ages. He was never affectionate and did not play with toys, which he always broke when possible. He was a very nervous child, and used to cross the street to avoid meeting a person. He attended an ordinary school, but the teacher considered him unsuitable for education and that he should be taken from school and sent out to work. However, he is able to read and write perfectly well and evidently learnt something there. At the age of 14 (1918) he heard the guns and rushed home saying they were after him and wanted to kill him. He was evidently beyond control because he was taken to a "padded cell" at the Shoreditch Infirmary. It was intended to send him to a mental hospital, but the mother took him home and looked after him for 15 years. The mother would not let him go out to work because people laughed and made fun of him. He wandered away from home in 1939 and was missing for 3 years. He was eventually found by the Salvation Army at Battersea. Admitted to this institution in 1944.

Present condition.—Clean in habits. Entirely unemployable. Able to read and write. Occasionally can be made to carry on a conversation, but never does so spontaneously and usually refuses to converse. It was surprising that he co-operated for a full hour of mental testing. The intelligence quotient on the Wechsler-Bellevue full Scale was 97. On a previous occasion it had been impossible to gain his attention.

He is hallucinated and deluded. His delusions are paranoid. He thinks people are after him—he wants the protection of C.I.D. and so on. His delusions are unsystematized, vague, variable, and not directed against anyone in particular. He does not show anxiety now in his behaviour. He is quite solitary, and stands about by himself in the ward, sometimes talking to himself. No catatonic symptoms. No impulsive outbursts.

Progress.—No change.

Family history.—Parents normal so far as can be ascertained. The father's sister was for years in a mental home and died there. Nature of condition uncertain.

Diagnosis.—Childhood schizophrenia. Onset probably at an early age with exacerbation precipitated by external events at the age of 14 years. Paranoid symptoms constantly in evidence. Considerable dementia. Mental grade within normal limits.

Cases in which it is Not Certain that Schizophrenia is Present without Original Defect.

CASE 9.—M. N—, female, aged 16 years.

Information scanty. Weight 6½ lb. at birth. Teething at 8 months. Learned to walk probably between 1 and 2 years. When a few years old said "Mum" and "Dad" and one or two words, but soon stopped talking and has never done so since. Has always been oblivious to others and lived entirely in a world of her own. However, a younger brother was born when she was 6 years old, and she was sufficiently aware of and concerned about the implications of this to be spiteful and aggressive towards him. From an early age was restless in her sleep, kicking and struggling sometimes. Also started attacks of screaming in the daytime. Never played with toys.

Present condition.—Functions at an idiot level. No speech and is incontinent. Sits huddled up on the floor in a corner of the ward, taking no notice of anyone. Sometimes runs quickly across the room to another corner in order to escape people. Sometimes views the observer viciously out of the corner of her eye, but is never aggressive. Has not got "the idiot look." From time to time claps her hands to her ears and screams, perhaps for as long as a minute. Apart from these attacks

she is motionless and quiet. No hyperkinesia, finger mannerisms or catatonic posturing. There is all-round reduction of activities and withdrawal.

She has remained in this state without change for the few years that she has been in the institution.

Family history.—Parents believed to have been normal. The mother's father was insane and died in a mental hospital. No history of mental deficiency.

Diagnosis.—Childhood schizophrenia of very early onset. Functions at an idiot level.

CASE 10.—B. W—, male, aged 14 years.

An illegitimate child. Mother attempted to strangle him when he was 3 months old. He was breast fed for the first 3 months, and was then taken away from the mother and put under the care of a foster mother who already had his older brother. At this age he "just lay and stared as if he were blind." He was investigated at the North Middlesex Hospital and no physical abnormality could be detected. At 6 months the mother thought he must be deaf, as he took no notice of his surroundings whatever. At 9 months he began to hold his ears and to make noises like the mooing of a cow. Also described as like a dog howling. These noises got steadily louder. From this time onwards the patient began to take much more notice of things and people, and at 12 months he was able to say "Mum" and "Dad," and "Pretty." He learnt to walk at 15 months old. He was a big baby, good tempered and rarely cried. He was admitted to this institution at the age of 2 years.

Present condition.—Functions at an idiot level. Incontinent. Never been known to speak. Is in almost constant movement throughout the day, walking or running from one place to another, or else standing and making strange gestures and faces. He frequently makes gestures with his arms and hands, with accompanying facial expressions as though he is an actor or adopting some oratorical pose. His behaviour, that is to say, is histrionic with a strong attitudinizing quality. The facial expressions adopted are, sometimes, quite good representations of normal expressive behaviour.

He also, sometimes, dances up to a person, touches him lightly and dances away gesticulating. Apart from this he takes no notice of people and never plays with other children. During his restless behaviour he is silent, in fact almost stealthy, uttering no sound and moving swiftly and quietly. He is not impulsive or aggressive. Occasionally he claps his hands to his ears and screams.

Progress.—No change since admission.

Family history.—The mother has schizophrenia of long standing and is now in a mental hospital. The elder brother is normal.

Diagnosis.—Childhood schizophrenia of catatonic type, which may or may not be superimposed upon organic defect. Mental grade of an idiot.

DISCUSSION.

These last cases raise a difficult problem: that of determining whether schizophrenia of very early onset is present alone or whether it accompanies organic defect. That a patient may demonstrate schizoid traits so soon as infant behaviour is sufficiently differentiated to reveal them is certain, and this presents no diagnostic problem if the tendency is not pronounced enough to hinder mental maturation in early life, but if it is so severe as to prevent the development of subject/object relations during the first year of life, it may be impossible to know if the schizophrenic process is acting alone or not. This may seem an academic problem—perhaps the distinction we are attempting to make is one that cannot even be clearly defined, for we do not know what schizophrenia is. Nevertheless it is interesting to speculate on this matter, and to do so may suggest certain lines of research. That an affective-conative disorder is fundamental in schizophrenia is probably implicit in the concept

of schizophrenia held by most psychiatrists, but the common assumption that mental deficiency and psychosis are two different dimensions may need qualifying. In an adult, mental functions are well differentiated and memory and mood may be disordered independently of one another, or thought processes may be distorted by affective interference, and yet mental tests which test intellectual capacity on affectively neutral ground show it to be fundamentally unimpaired.

In the infant this differentiation between one function and another has not occurred. From the earliest times a suitable affective-conative attitude is necessary in order to *perceive*. An unfavourable attitude, as apathy, impulsiveness, anxiety, may hinder understanding. A very unfavourable attitude may prevent entirely an adaptive outlook and the development of the proper subject/object relationship. When that is so, the infant sometimes not only fails to develop normal object relations, which is a negative finding, but does develop abnormal object relations, which is a positive finding, and especially characteristic of schizophrenia. On the whole, the principle behind these abnormal relations lies in their greater value for affective expression and less adaptive value to reality. In mental defectiveness there is every degree of affective-conative interference with the mental growth from slight to complete, and in any case it may be difficult to estimate the psychological causes of defect. Not only are there many organic causes of mental deficiency, but there may also be psychological causes, that is to say, disturbance on the psychological level which interferes with the growth of understanding.

In the last case described (B. W—) it is worthy of note that the first sign of expression at 9 months was qualitatively abnormal. It was not merely the late appearance of what normally occurs, but a *bizarre* form of behaviour.

The subject raised here is beyond the scope of this paper, but suggests that detailed investigation of the development of mental defectives during the first year would repay study. How often is development retarded, and how often is it different?

The cases included in this series are analysed in Table I. Symptoms common in adult schizophrenia were displayed in some cases, paranoid, hebephrenic and catatonic features being all represented. Bizarre play was noted in the past history of one patient, who used to spin tops in queer ways with rare skill. Despert draws special attention to "dissociation between language sign and language function," characterized by exceptional capacity to retain words, while the vocabulary for expression of needs is small. (This peculiarity is also a common feature of what Kanner later described as "early infantile autism"). A history of it was present in one of our cases.

The above-mentioned symptoms crop up here and there, usually in mild degree, but the typical patient is the one with schizophrenia either setting in at a more or less definable age, or else there was no age at which the patient seemed normal, and progressing insidiously, without episodes or process symptoms. The psychosis may proceed to considerable dementia, or only to dementia of mild degree, rendering the patient dreamy, withdrawn, friendless and unemployable. He is without ambition, quiet and uninterested in the affairs of the world. Usually his habits are clean and he dresses himself, but is

TABLE I.

Name.	Sex.	Age.	Age at onset.	Type of disease.	Sphere of symptoms.	Progress in last 5 years.	Mental level.	Heredity.
D. A—	M.	49	5-10?	Simplex. Slightly obsessional	I	No change	I.Q. 92	Unknown.
C. L—	M.	30	10-11	Simplex. Slight paranoid tendency	I	"	Feeble-minded	Mother has paranoid schizophrenia.
L. V—	M.	62	10-11?	Paranoid	I	"	I.Q. 90	None.
N. G—	M.	21	3-4	Simplex. Obsessive ruminative tendency	I	Slight deterioration	I.Q. 85	Father had paranoid schizophrenia.
A. N—	F.	21	5-10	Simplex. Was once slightly paranoid	I	Some deterioration	I.Q. 49	None.
B. H—	M.	27	10-12	Simplex. Paranoid tendency	I	"	I.Q. 80	Father schizoid personality type.
S. S—	M.	20	2-3	Simplex	—	"	Feeble-minded	Mother shy and withdrawn. M's. sister shy and nervy.
F. S—	M.	46	5-10?	Paranoid	I	No change	I.Q. 97	Father's sister died in mental home.
J. H—	M.	21	3-5	Hebephrenic	V	Slight deterioration	Feeble-minded	None.
H. J. C—	M.	20	3	Catatonic	M	Considerable deterioration.	"	"
J. P—	F.	19	10-11	Paranoid	I	No change	"	Unknown.
V. W—	M.	21	3	Hebephrenic	V	"	"	None.
J. A—	M.	10	2	"	VM	"	Imbecile	"
M. B—	F.	18	5	Simplex	—	Considerable deterioration.	"	Unknown.
A. D—	F.	21	11-13	"	—	"	Feeble-minded	None.
G. C—	M.	29	6	Hebephrenic	—	No change	"	"
C. E—	M.	50	10-13	Paranoid	I	Some deterioration	"	Unknown.
R. T—	M.	11	5	Catatonic	M	No change	Imbecile	None.
B. W—	M.	4	Under 1 year	"	M	"	Idiot	Mother has paranoid schizophrenia.
M. N—	F.	16	Under 2	Simplex	—	"	"	M's. father died in mental home.
G. S—	M.	14	Under 2	Catatonic	M	"	"	None.

Order of cases corresponds to degree of dementia, least demented and best preserved personality being first. Below the line are cases in which it has not been possible to exclude original defect.

Symbols of "Sphere of Symptoms": I = Ideational. V = Verbal. M = Motor.

TABLE II.—*Results of Tests with Wechsler-Bellevue Scale carried out on Six Patients with Schizophrenia.*

Name.	Intelligence Quotient.			Inter-test Scatter.		Deterioration.
	Full scale.	Verbal.	Perform.	Verbal.	Perform.	
D. A—	96	102	92	+	+	8.4
L. V—	82	90	77	++	0	14
N. G—	85	104	67	++	+	59
A. N—	49	52	54	+	++	0
B. H—	80	91	72	++	+	13.8
S. H—	97	99	97	++	++	25

TABLE III.—*Results of Tests with Wechsler-Bellevue Scale carried out on 58 Mental Defectives.*

Number of cases.	Verbal above perform.	Perform. above verbal.	Verbal. Scatter.			Perform. Scatter.			Arith. low.	Deterioration.	
			V +.	V + +.	Total.	P +.	P + +.	Total.		5-20%	Over 20%
58	26	28	34	10	44	30	8	38	41	12	26

loth to get up in the morning, late for meals, and only does ward work under supervision. The picture is that of schizophrenia simplex with all-round reduction of interests and activities, loss of affective contacts and of social integration. In adult life they may develop mild paranoid symptoms, or be prone to obsessive ruminations and scholastic interests which serve to localize their dreams and ruminations, giving them some semblance of reality and form, but distracting them further from contact with the world instead of relating them to it.

This series reveals a few points of special interest :

(1) The series as a whole shows no special tendency to motility disorders, although the occurrence of motor symptoms in childhood schizophrenia is usually given special emphasis in the literature. Only one case shows hyperkinesia, and five in all show catatonic motor symptoms. The question arises as to whether these symptoms are outgrown and replaced by others. This problem is discussed below.

(2) It has commonly been stated that paranoid symptoms are rare in childhood schizophrenia. They are present in four cases, but in all these paranoid symptoms did not appear until adult life, although schizophrenia began in childhood in three of these cases for certain and probably in the fourth. The paranoid symptoms are, in all cases, simple and unsystematized. Patients displaying these symptoms are all testable, and the intelligence quotients vary from 80 to 97.

(3) Evidently childhood schizophrenia is not necessarily a deteriorating disease. One patient has not demented in nearly forty years ; another, while able to give quite a good account of himself, has undergone a certain amount of deterioration during the past year, but the onset of the disease was at the age of three years, and he is now twenty-one.

(4) Affect is evident in several cases, although often somewhat flat, and *rapport* usually impossible. Anxiety absent in the adults, but present in one child. Three children and four adults are entirely solitary in habits.

(5) The characteristic thought disorder of schizophrenia is not well developed in any of these patients. There is altogether a poverty of psychogenic elaboration.

(6) Although a few patients vary from time to time in the severity of their symptoms, none of them follow the episodic course characteristic of the condition in mental defectives described as an episodic psychosis or chronic hallucinosis.

(7) In respect of social adaptability the latter patients are much superior, on the whole, between episodes to the schizophrenics, not a single one of whom is capable of useful employment in the workshops or gardens, whereas a mental defective of imbecile grade can usually be far more usefully employed. Some high-grade defectives cannot be gainfully employed because their *conduct* leads to quarrels with patients and staff, sullen refusal, "going off in a huff," and so on. But their *work performance*, in the intervals, is of quite good quality. Interest and pride in work may improve them. The patient with schizophrenia cannot concentrate on a job of work, his attention wanders, he repeats the same thing mechanically again and again without relation to practical demands, he forgets, and does the wrong thing, he dreams and plays. *He takes no interest or pride in work, for work is not of his world.*

Unemployability in the presence of sufficient intelligence may rank as a symptom of schizophrenia in a mental defective institution. It must be remembered, however, that we are dealing with schizophrenics of long standing, who have not recovered and will never recover. It would be interesting to know if employability is of any value as a criterion of improvement among schizophrenic patients in mental hospitals.

INFLUENCE OF AGE OF ONSET.

In our opinion age acts chiefly as a *limiting factor*. If we divide symptoms for descriptive purposes into three spheres, psychomotor, verbal (echolalia, verbigeration, non-adaptive use of words) and ideational (bizarre ideas, obsessive ruminations, delusions), it is clear that before speech is established symptoms can only be expressed through psychomotor mechanisms, later, psychomotor and verbal symptoms may both appear, and, last of all, symptoms in the ideational sphere. The age of onset continues to act as a limiting factor right into adult life, for the result of the characteristic affective change beginning in childhood is a narrowing of the circle of social contacts. The personality of the patient, never having extended object attachments deeply into the affairs of society with its complex goals, competitive spirit and clash of personalities, gains but a slender hold on the fabric of reality. The clinical picture and psychopathology in adult life are correspondingly threadbare. There is a poverty of psychogenic elaboration, no florid thought disorder. Delusions

are simple and unsystematized, and there is very little drive behind them. Symptoms do not give the impression of arising out of localized and definable complexes. These, we suggest, arise when fairly good social integration with socially directed drives were in evidence prepsychotically, with definite goals and ambition and a well-developed self-regarding sentiment.

With the onset of psychosis in childhood this process of maturation has not taken place, affect has not been gathered, directed and specified in relation to particular systems of ideas and ideals, the well-worn themes of human frustration have never been composed; the superego is not sufficiently strong and defined to intensify and localize conflicts. Consequently the schizophrenic change inclines to be diffuse and uniform, and the mental organization which well-developed complexes presuppose is wanting and cannot be grasped by the psychotic process.

The poverty of symptoms of the mild, chronic child schizophrenic who reaches adult life may then be put down to the influence of childhood as a limiting factor, but it may with equal truth be said that the complexity and variety of the symptoms of adult schizophrenia are due to the pathoplastic effect of adulthood and further, of adulthood in a modern western society, for it may be quite different elsewhere.

We cannot do better at this point than quote Ssucharewa, whose vivid description of childhood schizophrenia applies to a number of our cases. [Childhood schizophrenia] "shows a course like that of schizophrenia simplex, and is of interest as the fundamental symptoms of the disease are seen quite clearly. They are so well pronounced because the accessory symptoms and wall of psychogenic superstructure which conceals the basic symptoms in the psychopathological picture of adult schizophrenia is absent in these cases. One sees here with special clarity the successive stages in which the diffuse schizophrenic alteration in the whole personality of the child develops. The normal childish activity suffers first, and the affective contact with the surroundings; the liveliness and directness of the child's experience and the joy in creative activity disappear. The impulse to be busy with this and that which characterizes the healthy child becomes replaced by empty chatter, hollow reasoning and compulsive thought, which demonstrate the typical schizophrenic thought disturbance. Thought becomes empty, formal and unplastic, thought processes tend towards automatisms and stereotypies. The affective connection with others is gradually dissolved, tenderness towards the parents disappears, and the child, which a short time before had been mild and tactful, becomes rude, egoistic, and gradually develops a circle of personal interests which are largely unreal and little adequate in relation to the child's age (various calculations, astronomical studies, calendar studies and so on). The lack of unity of mental functions so characteristic of the schizophrenic process is the earliest symptom in our cases. To teachers untrained in psychiatry these children seem striking and strange. What strikes them is the unexpected and unpredictable absurdities of their acts, their unemotional impulsivity, their unmotivated obstinacy."

This description of the typical case could hardly be bettered. It only remains to mention that there is every gradation of chronicity and severity,

and in our experience, rudeness, foolishness and unmotivated impulsivity are early hebephrenic symptoms, and indicate that the disease is of moderate severity, and there will be moderate dementia. The milder cases are better able to give an account of themselves, to co-operate in mental testing, show apathy rather than foolishness, and are seldom impulsive. They may develop bizarre interests such as those described by Ssucharewa.

It is generally agreed that the chronic form is the commoner in childhood, and the acute form more devastating in its effects. Age does not seem to play an important part in determining the intensity of the disease process; that is to say, with onset at any given age, the disease may be mild or severe.

It is evident then that there is a relation between the age of onset and the *form* of the disease, but not between age of onset and *intensity* of the disease process. There remains to consider the effect of age on *degree of mental defect*. It is obvious that for disease of any given intensity, the younger the onset the greater is likely to be the resulting defect. Severe disease at two years will result in idiocy, while severe disease at nine will not be likely to result in complete loss of speech and of all social contact. Here, again, age acts as a limiting factor, for a psychosis which prevents mental progress entirely will result in a greater degree of defect the earlier the stage of mental development.

INFLUENCE OF THE SEVERITY OF THE PSYCHOSIS.

Intensity is, in our opinion, as closely connected with the form and course of the disease as the age of onset. For, as already mentioned, when the age of onset is, for instance, at three years, that fact in itself does not entitle us to predict what the outcome will be. Severe disease will result in extreme defect, all mental development being entirely halted, with loss of recently acquired contacts and regression to even more infantile modes of behaviour. A mild and insidious affliction starting at the same age will be compatible with development in some directions, even with a degree of educability at school age. The degree of mental defect is, therefore, determined by intensity at least as much as by age of onset. The degree of dementia is also decided by intensity rather than by age, for there is no special tendency of schizophrenia of early onset to proceed to severe dementia, judging by our cases and by reports in the literature.

Intensity also plays a part in determining the symptomatology. We have a strong impression that psychomotor symptoms are more likely to occur in acute and severe cases. They are not present in the mild and chronic cases. If age were an important determinant of symptoms, one might expect a patient first to display psychomotor symptoms and then outgrow them in place of verbal symptoms, and outgrow them again in favour of ideational symptoms, the psychotic process grasping each new mental function as it appears on the horizon of maturity. This has not been found, except in the tendency of mild cases to develop sometimes paranoid features or obsessive ruminative tendencies. On the contrary it is interesting that in *mild* cases symptoms in the ideational sphere (the highest mental functions) may occur at a very early age. Even in adult life the acute form is more likely to affect the lower psychomotor functional level (catatonic).

The connection between intensity and the form and outcome of the disease appears to be somewhat as follows :

(1) *Mild.*

Insidious onset. Schizophrenia simplex is the typical form. Simple paranoid tendencies may develop later and obsessive ruminative thought content. Fairly good preservation of personality.

(2) *Moderate.*

Hebephrenic features quite common, often combined with catatonic features. Symptoms in verbal and psychomotor spheres (J. H—, V. W—). Difficult or impossible to converse with. Sometimes able to read and write.

(3) *Severe.*

Psychomotility disorder, hyperkinesia. Idiocy. No speech. Incontinence.

This is a broad generalization and there are exceptions to this scheme. In making it the author wishes to avoid arguing in a circle. Some of the symptoms said to characterize severe cases are themselves criteria of severity, and therefore, to note their occurrence in severe cases is only to *define* what we mean by "severe" and not an addition to knowledge. The author judges severity by the degree of social adaptability. The absence of personal habits of cleanliness and the inability to make any social contact whatever constitutes severity. Such cases commonly display psychomotor symptoms. Mild ones, however, those that maintain some degree of adaptability, more usually have symptoms in the ideational sphere and motor symptoms are wanting.

RELATIONSHIP BETWEEN PSYCHOSIS AND STAGE OF MENTAL MATURATION.

Bender describes three critical periods of life at which schizophrenia may set in. These are the first two years of life, from 3-4½ and from 11-12. A number of our cases first showed gross abnormalities at from 3-6 or from 10-13 years. The first period (2-4 years) corresponds to what Bühler and others have designated the "*Trotzphase*" (phase of defiance), a stage of ego development at which the child first appreciates, as it were, its own will struggling against the will of the world to get the satisfaction of its needs, the age at which the child realizes it cannot always have everything it wants. At this stage that original spontaneity, that utterly genuine expression of affectivity born of a mind that never questions its part, but just plays it, has to be modified as a concession to reality. As noted by Lutz and others the child may become negativistic, speech may alter, there may be bed-wetting or rudeness and aggressiveness. Normally these symptoms disappear after some months, and no trace remains. What matters is whether or not a new reality relationship, a new adaptation is achieved. The failure of re-establishment of a proper adaptation may be the first sign of childhood schizophrenia (Lutz).

Although the onset of symptoms such as worried the parents occurred at about this age in quite a number of the cases of this series, peculiarities prior to that time were common. Lack of affection, no interest in toys, solitary habits and so on were frequently reported.

The nature of symptoms is obviously related to the cognitive powers of the child. The psychotic process can grasp only what is available, and especially what is just developing. As already mentioned, the symptomatology is also related to intensity, and if this is mild, functions, such as language, may develop unscathed, as had happened in a few of our cases with onset in the first few years of life. Otherwise, however, the relationship may be clear, and can be logically related to cognitive level. Prior to language development, symptoms are confined to the psychomotor sphere or appear only as withdrawal. Bizarre behaviour reveals the body itself or perhaps one or two toys as the objects of an abnormal relationship. With the beginning of language, words themselves may be the objects of an abnormal relationship, and language used non-functionally. With a little more development ideas may be the objects of an abnormal relationship, of which the patient N. G— is a good example. A bizarre interest in language itself is an earlier symptom in terms of mental maturation than bizarre ideas (which use language as a transparent medium), and would seem further from reality. This series of symptoms corresponds to the widening circle of cognitive growth and the corresponding embrace of larger portions of reality.

RELATIONSHIP OF SYMPTOMS TO PROGNOSIS.

The prejudice of our findings must not be forgotten. From the author's standpoint, even the mild cases are those eventually disposed of to a mental defective institution. However, we have the impression that hebephrenic and catatonic symptoms are of poor prognostic significance, and hyperkinesia and a wealth of psychomotor symptoms even worse. When symptoms are apparent in the ideational sphere only the prognosis is least gloomy, the mental level may be within normal limits, and social contact retained.

The consensus of opinion is that acute onset bodes ill. Body build may also be a prognostic aid. Three of our patients were markedly leptosomatic, with long slim hands and sharp, delicate features, small bones and slender build. All three showed hebephrenic features and were moderately demented.

DISCUSSION OF SOME POINTS OF SPECIAL INTEREST.

The general lack of drive behind symptoms and of evidence of well-defined complexes has already been mentioned. The fundamental affective change and altered relationship between thought and feeling has been present from an early age, and has prevented that organization of ideas in relation to society and consequent distribution of affect into specific directed drives upon the foundation of which characteristic thought disorder is built. There is a lack of so-called "symbolic thinking" in our cases.

Another point of interest is the worse prognosis of the acute form. As, according to Ssucharewa, exogenous factors play a bigger role in this form and the hereditary loading is less, the opposite might have been expected, and the explanation may be somewhat as follows:

Personality development consists of a steady growth of object relationships

and the formation of attitudes to the world's broadly recurrent happenings, whereby the maturing child becomes an integral component of society ; of the acquisition of social habits and of patterns of reaction, all of which are based on a structure that grows ever more firm, deep and indestructible. In the young child this process has not gone far, and acute symptoms, by their suddenness, are likely entirely to destroy the weakly founded, lightly impressed and recently formed personality structure with generalized loss of contact. In the adult, however, the basic personality structure, being far more deeply founded, remains and reasserts itself after the storm has passed. The psychosis was imposed on a relatively stable system able to revert to its former rhythm. The chronic and insidious form in the child is unable to obliterate entirely all channels of contact or obscure all object relations.

Some such explanation is required because, not only is the acute form of childhood worse than the chronic, but the reverse is true of adult schizophrenia.

There is hardly any tendency to an episodic course. It is interesting to compare this with pubertal schizophrenia (onset 13-17 years), in which the acute is commoner than the chronic form, and an episodic course is also common. According to Ssucharewa these episodes usually last from ten days to a few months, and dementia rarely occurs after the first one. As thus described, pubertal schizophrenia appears to have more in common with the episodic psychosis of mental defectives than with childhood schizophrenia or schizophrenia of adults. This may be because exogenous factors play a bigger part in both.

Although we cannot follow Neustadt, who believes that propfschizophrenia never occurs, it is nevertheless likely that its frequency has been exaggerated. Careful histories of the early years of life and mental tests would, perhaps, diminish the frequency with which the condition is reported. It is the author's impression that at this institution there are more cases of childhood and pubertal schizophrenia without any fundamental intelligence defect than there are of propfschizophrenia. The connection between schizophrenia in previously normal people, propfschizophrenia and the episodic hallucinoses is of considerable interest, but beyond the scope of this paper.

The opinion expressed by various authors that cases of childhood schizophrenia are not uncommon in mental deficiency institutions finds confirmation in this paper. As suggested by Despert, these patients may present as educational problems, and may not be seen by a psychiatrist before admission to a mental deficiency institution.

PSYCHOMETRY.

It was possible to test six patients. The Wechsler Bellevue scale was used. The results are recorded in the table. Wechsler describes in his book some characteristics of the psychometric pattern of schizophrenics, amongst others superiority of verbal over performance ability ; wide inter-test scatter, deterioration in some cases, low score on the digit symbol, and usually lower score on object assembly than Kohs Block designs. The table shows that five out of six show verbal superiority, scatter (especially verbal) and deterioration. Deterioration is measured by the Hold-Don't Hold test, and corrected for age.

Scatter is scored as + if any test score differs by 2+ from the mean test score, and ++ if it differs by 4+ on weighted scores. Verbal and performance scales are treated separately in the table for inter-test scatter.

The series is small, but the results tend to agree with those reached by other workers. That is to say, the pattern accords with that for adult schizophrenia. The least characteristic result is that of A. N—. This patient is shy and was nervous during the test. Her ability to read and write is unusually good for one with so low an I.Q.

According to Earl (1937, 1940) the performance capacity of stable mental defectives is usually superior to the verbal capacity, and the opposite finding is of bad prognostic significance. He notes that performance tests test intelligence in operation, whereas verbal tests rather test the results of past intelligence. Consequently non-cognitive functions are more likely to act as a disturbing factor in performance tests. These conclusions of Earl were not based on results with the Wechsler Bellevue scale. Results of mental tests using this scale on the last 58 admissions is given in the accompanying table for comparison. The number of testable schizophrenics here has been, of course, too small for general conclusions, but study of the results shows that the findings of other workers with this test that schizophrenics do better on verbal than performance tests, show scatter, and often considerable deterioration is no help in differentiation within an all-purpose mental deficiency institution. Mental defectives who are not schizophrenic are quite often superior on verbal tests, and show deterioration on the Hold-Don't Hold test. The reason for the latter very likely is different from the reason for deterioration in other conditions. Arithmetical ability is almost constantly low in both groups, and both groups show scatter. It is possible that scatter is wider and more constant, digit symbol scores more often low, and vocabulary more often high in childhood schizophrenia, but no definite conclusions on these matters is justified by our findings. The especial value of administering mental tests is that patients who, judging by behaviour and work performance, appear to be intellectually defective, are thereby shown to be endowed with an intellectual capacity within normal limits. Where a history is scanty and difficult to obtain, it settles the problem of "propfschizophrenia." Though we cannot follow Neustadt in his opinion that this condition never occurs, in our opinion the frequency with which it is reported would be much diminished by careful histories and mental testing, where possible. A number of cases diagnosed as propfschizophrenia might be shown either to have been normal in infancy or else still to be normal on mental tests.

Finally the criticisms some authors have made of judging intellectual capacity by school records receives further justification here. Many cases had a poor school record.

HEREDITY.

Ssucharewa, Lutz and others have found hereditary loading, more often collateral than direct, to be heavy in the chronic form. In our cases the mother of two patients and the father of one had schizophrenia. The presence of psychopathy was established in a number of other cases, but the nature of the

condition could not always be ascertained. It may also be of interest to workers in mental deficiency to note that the intelligence, education and social standing of the relatives is superior to what one finds amongst the parents of the feeble-minded.

Whereas a family history of psychosis is common in this series, there is not a single instance of mental deficiency amongst the relatives.

RELATIONSHIP BETWEEN MENTAL DEFICIENCY AND CHILDHOOD SCHIZOPHRENIA.

It is not within the scope of the paper to delve deeply into this problem, which can, however, be outlined by this question.

Is there any special tendency for mental defectives to develop schizophrenia? Statistical studies that might demonstrate greater or less frequency of schizophrenia amongst mental defectives are difficult to carry out. Defectives with schizophrenia would naturally be concentrated in institutions, for, other things being equal, they are more in need of care than those without it. Statistics would not reveal whether there is some particular type of mental deficiency strongly liable to schizophrenia, in the same way as mongols are prone to develop pulmonary tuberculosis. (Incidentally mongols may be strongly resistant to this particular psychosis. They rarely get it and are extraverted personalities.) Nor do we know of any patients with phenylketonuria and schizophrenia. Those with epiloia are frequently psychotic. Glaus has described a type of childhood schizophrenia in which he regards mental deficiency as the central and presenting symptom ("*Schizophrene Frühdemenz*"). There are a few cases at this institution which accord somewhat with his description, but they have not been included in the present study.

SUMMARY AND CONCLUSIONS.

The purpose of this paper has been to investigate the occurrence in a mental deficiency institution of patients afflicted with childhood schizophrenia in the absence of original defect, to take note of the route by which these patients reach their final destination, and to discover the usual course which the psychosis follows and its effect upon the mental level. In particular the following facts emerge from this investigation:

(1) Patients with childhood schizophrenia are quite often disposed of to mental deficiency institutions. They are usually not diagnosed as such or seen by psychiatrists before admission. Most often they present as behaviour problems to the parents or educational problems to the local authorities, and are diagnosed as mentally defective without further qualification. (This state of affairs may have altered during recent years with the growing interest in childhood psychosis and increasing number of Child Guidance Clinics.)

(2) The predominant type is probably that which resembles in essentials schizophrenia simplex, although paranoid delusions and obsessive ruminative tendencies are sometimes mildly evident. Patients of this type are also the ones that reach the highest mental levels. (The word "mild" is

justified within the context of this investigation. Naturally even these are complete and permanent losses to society.) Somewhat less frequent are cases of medium severity which often have hebephrenic features. The severest cases, functioning at an idiot level, are not reliably represented in respect of frequency in this investigation. Psychomotility disorder may characterize the more severe cases.

(3) Ineducability and unemployability in the presence of adequate intelligence is a diagnostic criterion which aids in distinguishing these patients from mental defectives.

(4) Patients who develop childhood schizophrenia do not necessarily dement, or they may only do so after having remained for many years in a stationary condition.

(5) Even when the onset is in infancy, intelligence, as judged by mental tests, may be within normal limits.

(6) The influence of age on the form of the disease is quite considerable, but it acts chiefly as a limiting factor. It is not related to an important degree to the severity of the disease.

(7) Acuteness and intensity are also important determinants of the form and course of the disease.

(8) As mentioned above, patients are often not seen by psychiatrists before admission. If such patients constitute an appreciable proportion of all cases, then published figures of the frequency of childhood schizophrenia are unreliable, for they do not include these patients.

The results of this investigation suggest that as some mild cases remain stationary until adult life and then deteriorate, they may not be recognized until adulthood. Careful early histories of patients in mental hospitals might reveal the existence of such cases. As with so many other scientific problems, the ground can be fully covered only through the co-operation of psychiatrists working in different fields.

Schizophrenia is a widespread disorder, and a study of its occurrence in different cultures might throw light upon its nature. For this purpose the terminology of Ackerknecht will prevent many pitfalls. The condition is of especial interest because of the way in which its form is influenced by the context in which it occurs—by the personality type, the age of the patient, the mental grade, the pattern of society—and consequently it requires investigation in its relationship to every context in which it occurs, and may indeed teach us something about the contexts themselves which we did not know before.

This paper is intended as a contribution to the problem of childhood schizophrenia, which is a fragment of a much larger problem—that of schizophrenia itself.

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MENTAL DISEASES PECULIAR TO CERTAIN CULTURES: A SURVEY OF COMPARATIVE PSYCHIATRY.

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MODERN psychiatry has developed in Western Europe, largely under French and German aegis, and latterly in the United States. It is pertinent to ask, since it deals with human behaviour in all its variety, if the concepts, working principles and empirically derived conclusions of psychiatry possess universal validity, wherever it might be practised. As one instance of the influence of cultural environment on psychiatric symptomatology (and also psychiatric practice), we may point to the "hysterogenic points" so often found in French hysterics by the Salpêtrière school of neurologists, who could provoke an hysterical attack or sometimes abort one by pressing on these points. Just across the Channel in England, among English hysterics, these phenomena could not be reproduced; they were, of course, special features of the disease, exhibited only in the atmosphere created by Charcot and his colleagues at that period. The psychiatrist in cultures farther removed from the civilization of Western Europe may well have reason to pause and ask if the principles and practice of orthodox psychiatry possess the same degree of truth or usefulness elsewhere than in Western Europe or America.

Margaret Mead recently spoke of "psychiatric imperialism" on the part of her American colleagues (1)—a peculiarly trans-Atlantic phrase, but one perhaps effective in emphasizing that psychiatric thought originating in Euro-American culture, need not be the alpha and omega of psychiatry everywhere. Another American, E. H. Ackernecht, protests against the egocentricity of Western thought: "Our culture," he says, "is unique in its . . . outlawing of the irrational, the emotional, the ecstatic. These phenomena have thus become most incomprehensible and unknown to our society. The bedroom, the liquor store and the office of the psychiatrist are their last sanctuaries, but only the last of these three places is not tabooed for public expression. Thus it is no wonder that an almost unlimited number of phenomena have acquired a psychopathological label." He mentions how primitive religion has been called "organized schizophrenia," magic "the pathology of culture," the savage "an obsessional neurotic," and the medicine man of primitive tribes described variously as epileptic, hysterical, or suffering from neurosis (2). He concludes: "It needs the gigantic helplessness and vanity, the terrible uniqueness of our culture to come to such statements."

Emil Kraepelin, the founder of modern psychiatry, was probably also the first to inquire into the possibility of a science of comparative psychiatry. He introduced that term (*vergleichende psychiatrie*) in 1904 to denote the study of mental diseases as they manifested themselves in different cultural groups (3). He himself, a lover of travel, had spent some time in Java and India studying

insanity. Following the example of his classical *Lehrbuch*, most text-books devoted a section to the influence of culture on mental disease, but more often than not this contained merely an undigested and ill-assorted miscellany of observations by untrained or poorly trained workers, too ready to see correlations where there were none, or draw conclusions where none could be inferred. For example, ever since Krafft-Ebbing's famous observation on "civilization and syphilization" many curious statements have been made on the alleged absence or rarity of general paralysis of the insane in non-Western cultures.

Moreover, attention was paid to the nutritional, toxic and climatic aetiological factors, rather than to the strictly sociological factors of psychological significance which may cause or modify the picture of insanity. The latter are no doubt much more difficult to investigate.

THE MEANING OF THE NORMAL.

The problem of the definition of abnormality comes to the fore, once we turn from the organic reaction types to the schizophrenic and affective reactions, where reactive psychogenic factors play a significant part in the pathogenesis. Here no simple physico-chemical, biological or anatomical test can establish an abnormality. The disease itself can only be defined against the social background; thus even the deformed foot caused by the practice of foot-binding—specimens of which grace many a pathological museum in the West—cannot be simply regarded as abnormal without taking into account the social and cultural *milieu*.

Theoretically, the concept of abnormality is both peculiar and confused, because in it are contained two different notions; on the one hand, there is a judgment of value, of goodness or badness; on the other, there is a reference to the statistical average. If we keep in view the *ideal* functioning of body and mind, then the actuality must fall short of the ideal, since the majority of men and women cannot possibly function in the ideal manner. The majority also constitute the average, which is, from the statistical point of view, the normal or the healthy. Paradoxically, then, the normal or healthy is that which is not functioning in the ideal manner. (For a full discussion of this theme see K. Jaspers, 4).

It is desirable, therefore, when we say that a man is abnormal, to specify, firstly, how he departs from the average; and secondly, how he falls short of the ideal, then we are immediately faced with the problem, what average? and whose ideal?

To answer the first question, we may draw some help from the work of the school of anthropologists associated with the names of Mead, Benedict, Bateson, Boas and Linton. These workers attempt to describe the psychological characteristics of various patterns of culture, and even attempt to classify the latter into various psychopathological categories (e.g. as paranoid, aggressive, introvert or extrovert, megalomaniac, etc.). We may agree with B. Malinowski (5, p. 206, f.) that this approach is lacking in scientific objectivity.*

* Professor C. G. Seligman, for example, relates how with practical experience of the Chinese people he had to change his impression of them as introvert to the opposite view (6, p. 86).

and that the writers fall into the error of thinking that psychological normality is a special attribute of Western civilization. Clearly, the recognition of differences in the temperamental make-up of various peoples is of fundamental importance for comparative psychiatry.

What is needed is not a total rejection of this method of study, but the use of ordinary descriptive terms which do not drag in psychopathology, and, consequently, implicit reference to an arbitrary norm of human behaviour.

It would be a grievous error to suppose that if a certain form of behaviour in some culture or other resembles insane behaviour it is necessarily abnormal. For instance, if a Hindu fakir behaves much like a catatonic schizophrenic in Britain, he need not necessarily be insane; since not only can he begin or stop his apparently catatonic behaviour at will, but such behaviour has a recognized place, and possesses some degree of social approbation, in his own culture. Similarly, the Siberian Shaman may fall into a state of partial hysterical dissociation like the hysteric in, say, Britain, but this state he voluntarily seeks, and in doing so he obtains authority and respect from the tribe.

It is essential, therefore, to look beyond appearance and form, and inquire into function. We are brought back to the question, what is normal behaviour from the ideal point of view?

We need to concern ourselves with functional concepts like "adjustment," "integration," "adaptation," and "survival." In organic medicine the problem of what is not normal or ideal is relatively simple; he is not ideally normal, i.e. he is ill, who feels pain or fatigue, who does not live reasonably long, who cannot work or reproduce, etc. In psychiatry we tread on uncertain ground. Even within one culture, as Jaspers has pointed out, ideas of what constitutes abnormality may vary. Thus the patient with an hysterical headache following injury to the head during work, and expecting compensation, will be regarded as ill by the psychiatrist, but not so by the insurance company.

It is still possible to reach a conclusion as to normality or otherwise by thinking in terms of "adjustment" or "adaptation" of the individual to his environment. In social anthropology this method of approach has its exponent in B. Malinowski (*op. cit.*), who insists that every anthropological fact has meaning only when its function in the culture is appreciated. With this attitude, of course, the question whether any behaviour characteristic of a given culture is normal or not becomes meaningless, just as with the advent of psychoanalysis the difference between normal and abnormal behaviour is largely obliterated (cf. Freud's *Psychopathology of Everyday Life*). Deviation from the mean of any form of behaviour is unimportant, but rather why the deviation occurs. The quintessence of abnormality, as H. J. Wegrocki (7) points out, is the choice of a type of reaction which enables the individual to escape or fly away from a difficult situation instead of facing it squarely. The choice resulting from the conflict is, moreover, unconscious, and apparently beyond the will or purpose of the patient. It must be noted that the reaction which takes the form of flight must, according to the values of the society, be regarded as useless, non-productive, non-constructive behaviour. If this were not so, if it had instead social approbation, then it would probably be a form of "sublimation" (see later). In point of fact, social attitudes towards

unusual behaviour are changeable, and also often uncertain, so that it is not always clear whether a form of abnormal and unusual behaviour is diseased or not.

We need to consider here briefly the distinction between genius and lunacy. Both are departures from the mean. Unlike lunacy, genius is constructive, it extends the range of human experience, and it is valued and sought after by the community. A single individual may at one time produce work bearing the stamp of genius, and at other times fall into behaviour characteristic of insanity; and society may mistake genius for insanity or *vice versa*.

From the psychoanalytical point of view, a case can be made out for regarding the behaviour of genius as a "sublimation" of internal psychic conflicts. Unfortunately the concept of sublimation is far from generally accepted. Sublimated behaviour is simply by definition, socially valued behaviour substituted for similarly determined but less desirable behaviour, so that in the end we are not much nearer an understanding of the nature of genius. The philosopher C. Delisle Burns has tried to analyse the difference between genius and lunacy in general terms (8). He thinks that the genius is more co-ordinated in his behaviour, is more in equilibrium, makes more use of the conscious mind, and is generally more in contact with his fellow men than the lunatic. These distinctions are difficult to apply to concrete cases. They are probably true at their own conceptual level, but they cannot explain why, for instance, a dissociated person like the Shaman is treated as a genius in Siberia (see below), but would be regarded as a madman in Europe. The cultural background cannot be ignored. Both genius and madman are abnormal, since they are unusual as well as functionally unable or unwilling to adapt themselves to Society. Society, however, adapts itself eventually to the genius, but does not do so in regard to the lunatic. However, each culture has *within limits* its own idea of what genius and lunacy consists in, and these ideas may also change with the times.

MENTAL DISEASES PECULIAR TO CERTAIN CULTURES.

We are now in a position to study various mental diseases recognized as specific to particular cultural groups. For the purpose of classification I propose to adopt E. M. Ackernecht's terminology (*ibid.*). He suggests the term "autopathological" to describe those conditions abnormal in the culture in which they are found, but normal in other cultures; and the term "auto-normal" to cover those forms of behaviour, normal in their own cultural *milieu*, but which, occurring in other cultures, would be regarded as abnormal, i.e. the behaviour is also "heteropathological." Similarly, the term "hetero-normal" is self-explanatory.

(a) *Autopathological and Heteropathological Behaviour.*

This class is the most important, since it comprises the majority of mental diseases universally recognized as such, at least, in their developed forms.

Among this group are also certain diseases distinguishable from the accepted major reaction types, which are peculiar to particular cultures, but which, if

they appeared in other cultural groups would, I think, also be called abnormal. These have been called "fashions in disease." It is characteristic of fashions that they change with time, and it is better to use that phrase for those mass hysterical outbreaks which, for instance, afflicted the medieval Europeans.

Psychic contagions.—These hysterical "contagions" were frequent in medieval societies, and still to be found now and then in closed, fervently religious communities like nunneries, where belief in possession by external agencies exists, or in small, compact communities of easily excited and emotional people, like girls' boarding schools. Thus there were in Europe dancing manias, children's crusades (cf. the legend of the Pied Piper of Hamelin), the Tarantism (a "dancing mania" provoked by the belief that such exertions will ward off death from the bite of the poisonous tarantula spider), and the choreomania or St. Vitus' Dance of those times. For a list of these epidemics in Europe from the later Middle Ages to fairly recent times, we may turn to K. Osterreich (9, p. 187, f). This author also mentions (p. 192) a case of epidemic zooanthropy occurring in a German convent, when the nuns believed themselves possessed by cats (or changed into cats), and behaved accordingly. Related to these are the epidemic hysterias manifested by the "Jumpers" and "Barkers" of the Eastern part of the United States. These assumed extreme and grotesque proportions at the turn of the eighteenth century, when, at revival meetings by camp-fires, tens of thousands of people, stirred by fiery oration, would jump, shout, bark and roll about in extreme religious fervour (D. W. Yandell, 10). Of the "Jumpers" and "Barkers" I shall have more to say later. To come to our own times, the occurrence of an epidemic of hysterical convulsions among the inmates of a girls' boarding school in Louisiana has been reported at length by E. A. Schuler and U. J. Parenton (11).

These epidemics must have been considered abnormal by many in their own times and within their own cultural settings. As psychological phenomena they are no doubt traceable to certain prevalent social attitudes and beliefs; and if these ideas, beliefs and attitudes become fixed so as to assume the significance of culture traits with some degree of permanence, it is conceivable that they may give rise to certain aberrations, which, persisting while the society as a whole undergoes development and change, and while knowledge advances, will become increasingly unusual and grotesque. The so-called possession by animals or the devil, accepted as part of the natural order of things in olden days, appears to us educated moderns as something definitely insane, although the idea of possession by the spirits of the departed still exists among the spiritualists in Europe, and among a rather larger proportion of the people of China, and is in no way regarded as a disease. The idea of the abnormal varies with the times.

An excellent example of a disease shaped largely by prevailing folk-beliefs is *Koro* or (in Chinese) *Su Yang*.

Koro or Su Yang.—This illness is known by the former name among the Malays, and by the latter among the Southern Chinese, especially the Cantonese. It has not been recorded among other peoples. The patient, usually a neurotic with sexual conflicts, e.g. over-impotence or masturbation, suddenly becomes seized with the conviction that his penis is shrinking into his abdomen.

According to popular belief, if this is allowed to happen, death ensues ; and the patient falls into a state of panic. He hastily resorts to various remedies. The orthodox way to forestall death is to clamp the penis in a wooden case used for holding a jeweller's balance (called in Cantonese *Leh Teng Hup*) ; or failing this, to tie round the penis a red string (among the Chinese), red being the colour successful in warding off evil. Sometimes instead of the above measures the wife immediately practises *fellatio*. Inevitably a great commotion is caused and the patient may be carried in distress to hospital.

That it is a psychogenic illness resting on superstition there can be no doubt. There is a wealth of folk-lore in connection with this disease, but it is probable that actual hysterical anaesthesia of the penis, or some disturbance of the "body image" occurs. G. Bychowski has described a case in a European corresponding exactly to *Koro* (12). It is said that a female form of the disease consisting in fear of shrinking of the breasts and genitalia also occurs. The best account of *Koro* is probably that of van Wulfften-Palthe's (13). Nosologically, *Koro* is, I believe, an acute anxiety state (panic) in persons with sexual conflicts and preoccupations.

Latah.—This is a comparatively well-known disease, first described among the Malay races, but it has become apparent that essentially similar diseases occur in many of the simpler societies under local names ; for example, as *imu* among the Ainus of N. Japan, as *myriachit*, *ikota* or *arctic hysteria* among the Siberian tribes, as *mali-mali* in the Philippines, *yaun* in Burma and *bah-tsi* in Siam. It has also been described in the Sahara desert, Italian North Africa, and the Yemen. (See references 14-20.)

The disease is probably a fright neurosis with marked hysterical features ; it is certainly not simple hysteria, as Kraepelin supposed it to be (21, p. 157). The patient, usually a middle-aged woman, when suddenly frightened, falls into a trance-like state in which she exhibits automatic obedience, echolalia and echopraxia. The stimulus may be of the most trivial kind, e.g. a sudden touch, the ringing of a passing bicycle bell, or even the mention of the name of a dangerous animal. In the *latah* state the patient is completely at the mercy of those who surround her, doing almost anything they command her to do, imitating all their actions, and, it is said, even the swaying of a tree bough or the mewing of a cat—but this is probably not true.

There is perhaps a special predisposition to fear, as van Wulfften-Palthe points out (*op. cit.*), but in younger women a brief exhibition of echo-symptoms when startled or suddenly embarrassed, as for instance, when tickled, may simply be a sort of affectation designed to attract attention. (*Latah* in Malay means ticklish, *bah-tsi* in Siamese means "tickling madness"). Many Malay women in the countryside show this and nothing more ; but some cases gradually progress until they become, after many years, permanently *latah* and prone to automatic obedience and echo-reactions, and they then tend to hide themselves from other people. These cases remind one of the "degenerative hysteria" of German authors.

It is possible that the social and cultural conditions in places where the disease occurs are such as to produce a certain passivity of mind and an unpreparedness for sudden decision and action, since they are far removed from the

noise and competition of modern civilization, but are at the same time not wild and menacing to their inhabitants. As regards proneness to fear, this is clearly seen among the Ainu. According to W. Winiarz and J. Wielawski (*ibid.*), these people have a special fear of serpents, and if one of them steps on a (serpent-like) snake, he will throw a full hysterical fit. It is possible to see how an hysterical attack can easily acquire mimic features when it is accompanied by some clouding of consciousness, as in this case, where the provoking cause is fear. The attack may become standardized by repetition, so that it may even become, in a sense, a culture trait.

Some authors, e.g. Manson-Bahr, van Loon and W. McDougall (16, p. 324, f.n.) have pointed out that the disease only affects Mongolian peoples, and point to race as a causal factor in its pathogenesis. That this cannot be so is proven by the occurrence of an exactly similar type of illness among the "jumping Frenchmen" of Maine (Beard, 22), sufferers from a curious disease, misidentified as convulsive tics, and as such repeated parrot-fashion from book to book, but entirely neglected by writers on latah. That this disease was described in temperate North America also disposes of the theory that extremes of climates are causative factors.

Miryachit may occur in epidemic form. An example is recorded of a regiment of Transbaikal cavalrymen who suddenly became echolalic and began to repeat the commands of their officer, and the more vehemently the officer reiterated his commands the more readily they were repeated (quoted by Czaplicka, *op. cit.*, p. 313). This resembles the psychic contagions, or mass hysterias.

The primitive hysterical outburst of undifferentiated excitement, weeping, laughter and running away, with or without hiding has been described among many of the simpler people, e.g. as *piblokto* among the Eskimos (A. A. Brill, 23) and as *misala* among the natives of Nyasaland (R. Howard, 24). The hysterical outburst (from which the lay connotation of the word "hysterical" is derived) also occurs in more advanced societies, though usually among the less intelligent and the poorly educated.

Amok.—This is an acute outburst of unrestrained violence associated with homicidal attacks, preceded by a period of brooding, and ending with exhaustion and amnesia. The fury of the patient may be quite undirected and he may strike down animals and men indiscriminately in his path. Such an acute reaction can obviously arise from many underlying causes. It has been ascribed to epilepsy by Kraepelin (21, p. 157), confusion from malaria or cerebral lues by F. H. G. van Loon (25), and by others to hashish poisoning, sunstroke and mania. It has also been suggested that this may be a primitive reaction corresponding to the outbursts of psychopathic persons in more developed cultures (J. C. Carothers, 26). Thus very similar attacks have been described in Polynesia and in the Sahara (*cafard, soudanite*). There is no doubt that amok-like attacks occur both in Europe and America.

Some authors, like van Loon (*ibid.*), believe that the reaction is specific to the Malays, but the ascription to race as such of definite causal significance is always dubious. Perhaps the more correct view is that of van Wulften-Palthe (*ibid.*), who calls amok a standardized form of emotional release, accepted

by the community, and indeed expected of the individual who is placed for some reason or other in an intolerably embarrassing or shameful situation. It is not simply a lack of power of self-control, since it is a mistake to equate deficient powers of inhibition as such with so-called primitiveness. Many outlandish tribes exhibit the greatest self-control, for example, when undergoing ritual tortures.

We should probably distinguish true amok as it occurs among the Malays from cases of acute confusion with paranoid and homicidal trends arising *per se* or as episodes in many different psychiatric reactions. The amok of the Malays probably has a social significance; for example, among the Moros of the Philippines cases of amok have been recorded which had worked themselves up by religious incantation and other prescribed rituals.

The Wihtigo Psychosis.—This is an illness confined to the Cree, Ojibway and Salteaux Indians of N. America. These people believe in the possibility of being transformed into a *wihtigo*, a giant creature with a heart of ice, who eats human flesh for food. During times of starvation, a man may suddenly develop a craving for human flesh, and also develop the delusion that he has been transformed into a *wihtigo*. This mythological creature is greatly feared, but sometimes actual cannibalism takes place, as though the patient were impelled towards the very behaviour that is feared. The belief is so strongly held that sometimes alimentary symptoms like loss of appetite or nausea arising from quite ordinary reasons causes the patient to fall into great excitement for fear of being transformed.

This illness is a good illustration of the effect of mythology and environment on insanity. Nosologically, it may perhaps be essentially hysterical in nature, like demoniacal possession. For an account see A. Irving Hallowell (27).

(b) *Autonormal and Heteropathological Forms of Behaviour.*

Among those types of behaviour which are normal in their own cultural settings, but which would be regarded as diseased in Euro-American civilizations, or for that matter, in Chinese civilization, are the following:

Homosexuality.—That homosexuality is accepted openly as a normal mode of behaviour in certain cultures, and also certain sub-cultures within Euro-American civilization is well-known. It was so accepted in ancient Greece, and if not accepted, it is at least looked upon with less distaste or surprise among, for example, the Turks and the Bengalis. The English public school system provides a *milieu* conducive to it. The degree to which it is regarded as an abnormality in various countries may be gauged by the attitude of the law towards it; I believe it is true to say that the Anglo-Saxon countries adopt a rather harsher attitude towards it than the Latin countries, and that Chinese law is rather more tolerant.

In certain cultures not only is the homosexual tolerated, but the homosexual actually obtains a position of power and prestige. Thus in N.E. Siberia the Shaman (or medicine-man *cum* oracle) of the Chukchis, are men who, in the process of acquiring shamanistic powers have, often suddenly, turned homosexual. More rarely, a woman may also become homosexual and then acquire all the prestige and influence of the Shaman (quoted by O. Klineberg, 28, p. 272).

Possession.—Many of the tribal medicine-man-oracles among primitive peoples fall into a state of trance, when they are believed to be "possessed" by a spirit, who speaks through them. The medicine-men of the Bataks of Borneo are of this type, though the majority of the Siberian Shamans are not. The phenomenon of possession is doubtless hysterical in basis; indeed, Osterreich in his classic book on this subject (9, Chap. 3) says it is identical with the phenomenon of somnambulism, a form of hysterical dissociation. In Euro-American civilization such a form of behaviour would be labelled pathological, except by cultural sub-groups like the spiritualists, or the Roman Catholic Church, which, I think, still believes in possession by the devil. It may here be pointed out that in China a form of possession-shamanism, the (Taoistic-Buddhistic) *Moh* or *Wu* priests, exists (see Osterreich, *op. cit.*, p. 355, f.). Similar phenomena are also found in India and Japan.

The Potlatch of British Columbia.—Among the Indians of British Columbia there is an institution called the "Potlatch" which is a recognized way of settling a quarrel by the destruction or distribution of property of any sort. The persons involved challenge each other to a duel in which each tries to destroy or give away more property than the other, and the one who succeeds in doing so is acclaimed the winner. This method of "fighting with property" is also known in Alaska.

During the potlatch the contestants make long speeches referring to themselves in excessively grandiose terms, which the orthodox psychiatrist might well describe as paranoid and megalomaniac. Moreover, among these people there is a great sensitivity to insult, so much so that every little misfortune or accident is looked upon in terms of an attempt to insult them. The only redress then is to challenge their fancied enemy to a potlatch. This kind of behaviour corresponds to that of a lunatic in a paranoid state in advanced cultures elsewhere.

Whether or not paranoia and paranoid states occur among them I do not know, but if they do there can, under such circumstances, be abnormal and deviant behaviour only if they are extreme or associated with definite depressive or schizophrenic symptoms.

An account of the potlatch may be found in a paper by R. Benedict (29).

The Touch taboos of the Dobuan Islanders.—Among the inhabitants of the Dobuan Islands there exists a general attitude of fear and suspicion each towards his neighbour. No one, for example, will touch or eat the food of another in case it might have been magically poisoned (see R. Fortune, 30). This is but one example of the many taboo systems commonly found in Polynesian cultures. The touch taboos are reminiscent of the rituals and prohibitions of our obsessional-compulsive neurotics (more especially of *défense de toucher*). Indeed the psychoanalytic theory of this neurosis takes into account the remarkable similarity.

Thanatomania.—This term has been used to describe cases of death occurring for no other possible reason than auto-suggestion, following the breaking of a taboo, the consequences of which is known to be death. Thus an untutored Maori may pine and die if he discovers that he has taken the chief's food, an infringement of a taboo which is known to be followed by death. This remark-

able phenomenon is thoroughly authenticated, and has been the subject of a paper by W. B. Cannon (31). Such a method of death, accepted almost as a matter of course by the Polynesians, would, if it occurred among us, arouse all the curiosity and amazement associated with the abnormal.

Yogism.—In spite of its exposition by many popular writers, there are included under this term phenomena of great psychiatric interest. Such, for example, are the catatonia-like postures assumed by the fakirs for long periods, sometimes for days on end, until, it is said, structural changes take place. By dint of long practice they are able to withdraw their attention from the environment, to remain in a state of intense self-absorption, in complete immobility, and apparently with suspension of basic physiological needs (see quotation from F. Alexander by Klineberg, *op. cit.*, p. 253). It may be pointed out that yoga practices also have a following among certain Taoist-Buddhistic sects in China. (C. G. Jung has studied this from the point of view of analytical psychology, 32.)

The Western psychiatrist would, if he took the static, structuralist point of view, classify all the above with the pathological. Conversely, many primitives would, according to their own standards and values, regard as diseased or abnormal certain forms of behaviour which are in the West regarded only as personality aberrations or, indeed, as entirely normal personality and character traits.

Under this heading might be mentioned the case of the unsociable girl of the Ga people (N. American Indians) described by A. I. Hallowell (33). She was regarded as ill and needing treatment, but such a girl in Europe or America would only be thought of as shy and retiring, perhaps a little schizoid.

R. Benedict (29) has also pointed out that the initiative and energy of the American, considered as a virtue by them, might well be regarded by the Zuni Indians as an illness or at least something abnormal (indeed, it would so be regarded by many Chinese of the old school!). Similarly the N.W. Coast Indians, used to throwing away their property at the potlatches, will not take for granted that the acquisitiveness of the modern civilization, East and West, is something only to be expected of human nature, as we ourselves implicitly do; to them our greed may savour of lunacy.

CERTAIN OBSERVATIONS AND GENERALIZATIONS.

We have already mentioned that the old notion that G.P.I. is rare in non-western countries is no longer tenable. There is no better illustration of the dangers of generalization about the incidence of a disease than in this instance. The exponents of the original view failed to take into account the many complex factors in the social environment that determine whether or not patients will present themselves at clinics for observation, and also the facilities which exist for such observation. For similar reasons, the parallel observation that the disease is more common among the educated (cf. van Wulfften-Palthe, 13) is suspect, because in societies like that of Java the educated classes are doubtless more ready to present themselves at hospitals, and being urban, can do so more easily. It must be remembered that folk-ideas and superstitious ways

of thought, as well as fear, are apt to cling round mental diseases more tenaciously than round bodily illnesses.

The reluctance of children to send their aged parents into a mental hospital arising from the tradition of filial piety, as well as the relatively smaller development of compact and restricted flat-life in cities, probably explain the apparent rarity of senile dementia in China; although it is true that care and comfort in old age may ward off senile dementia to a great extent. It is difficult to know what reliance can be placed on observations like that of J. C. Carothers (26) when he maintains that there is little hypertension and arteriosclerosis among the negroes of Kenya because there is seldom anxiety of any duration occurring in these people. Even if there is little arteriosclerotic dementia, the reason adduced for this is probably not true. It is facile to assume that because a society is primitive, it is necessarily less complex and that there are fewer causes for insecurity and anxiety. The savage seldom lives in noble and idyllic simplicity, either from the sociological or from the psychological point of view.

Many observers have pointed out that in the more primitive cultures schizophrenia is quieter, less florid, and is, in the words of Gordon, "a poor imitation of European forms" (cf., for example, H. L. Gordon (34), van Wulfften-Palthe, *op. cit.*). This is possibly true, since the richness of psychiatric symptomatology is dependent on the intellectual and cultural resources of the patient; the same difference is found between the educated and uneducated in any cultures, and sometimes the barrenness in clinical picture of insane Chinese peasants is striking. It must be pointed out that the psychiatrist studying patients whose language is unfamiliar to him is bound to miss a great deal in the way of symptoms. There is also a notion that paranoid schizophrenia is rare among the simpler peoples, in contrast to the catatonic variety. This could only be true if the people concerned were so primitive as to have only the rudiments of language. The more likely explanation for the difference, supposing it were true, is that the observer cannot understand what the patient says, and that possibly the patient is thereby discouraged from communicating his thoughts to him in speech.

The frame-work of the schizophrenic process remains the same wherever it is found. The classical dissociation of mood from thought, the ideas of influence and of passivity, the hallucinations and delusions, are constantly found. (For a study of the content of thought among Chinese schizophrenics see C. C. Kao *et al.*, 35, Chap. II.) Laubscher (36) has noted that among the Tembus in S. Africa schizophrenic delusions show a regression to tribal beliefs (the patient presumably having previously taken over modern or "Western" ideas in varying degrees).

Van Wulfften-Palthe agrees with Gordon that in Java and Kenya respectively, true manic-depressive insanity of the cyclic type is rare. Both van Wulfften-Palthe and Carothers (the latter working in Kenya) observe that mania is more common than depression, the first worker noting that mania is often associated with mental defect, and the second attributing the difference in incidence to the weak repressive powers of his patients. Van Wulfften-Palthe also mentions that in Java melancholia (depression) is rather commoner among the Chinese. Carothers finds that in his involutional melancholics there

is little idea or feeling of guilt, and he compares this fact to the observation of C. G. Seligman that in Japan delusions of a religious nature with guilt are practically absent, probably because Japanese religion is cheerful and not centred round the idea of sin.

Whether Carother's thesis is true, that mania is rare among his negro patients because they can so readily fulfil their desires in phantasy, thanks to the weakness of their repressive mechanisms, is certainly open to question. Carothers also declares that obsessional-compulsive illness is uncommon in Kenya because the society itself is obsessional-compulsive in nature, i.e. full of rituals and prohibitions. Here again language difficulty may obscure the recognition of obsessional symptoms, just as a stupid patient may be unable to describe his obsessional symptoms to the doctor, thereby helping to give rise to the impression that unintelligent subjects do not suffer from obsessional illness, a point which Aubrey Lewis emphasizes.

We must finally mention an important psychiatric generalization which affirms that there is an analogy between schizophrenic and primitive ways of thought. This was first exhaustively studied by A. Storch (37) more than twenty-five years ago, but for a recent study see J. Burstin (38). Where the Tembu schizophrenic regresses to his own tribal beliefs, the European schizophrenic regresses to what is very like superstition and primitive folk-lore and magic. The Chinese patient in his turn becomes preoccupied with ideas of possession by animal familiars, gods and devils, of magical influence, and of communication with many unseen spirits, all drawn from the animistic element still so strong in Chinese culture. There is a large literature on the nature of schizophrenic thought processes, and the *analogy* between primitive savage thinking and the regressed schizophrenic thinking is often striking. To say this, of course, is not necessarily to imply that the savage is diseased; but both he and the schizophrenic in fact do not make use of, or lack, the logic, the concept of causality and the capacity for abstract thought of the normal educated modern man.

PRONENESS TO CONFLICT.

Having seen how standards of normality differ from one culture to another, and how cultural conditions can influence the form and incidence of disease, we may now proceed to a more detailed consideration of the nature of "unhealthy" situations in various cultures.

Every cultural group contains within itself possibilities of mental conflict. While Freud holds the view that increasing civilization, since it is associated with various prohibitions, must be attended by discontent and mental conflict, he also points out that of the three sources of human suffering—that from our body, from the environment, and from our relations with other men—the most painful is the last (39, p. 28). It would be a mistake to think that "uncivilized" cultures are, therefore, necessarily simple in their interpersonal relationships, and that this source of pain is in them negligible.

Malinowski's study of the Trobriand and the Amphet Islands (40) has demonstrated that comparatively undeveloped societies may yet show a distinct difference in the incidence of psychoneurotic illness among them. Both

these peoples are of similar race and language. The former have generally a loose morality, with their children permitted a great deal of sexual experimentation, but the latter neither permit pre-nuptial intercourse, nor have they institutions to maintain what might be termed sexual license. Malinowski observed that the former people showed little in the way of neurasthenia, tic, or hysteria, compared with the latter.

Certain social customs and institutions serve to relieve accumulated anxiety, or prevent anxiety from accumulating, by making possible the expression of biological drives. Such are the cultivation of games of aggression, like boxing or wrestling, the toleration of adolescent sex-play, of organized prostitution, and of the orgy in various forms. Here we may also mention the use of intoxicants and other drugs like opium, which help to produce a withdrawal from the harshness of reality and soften the pain of emotional conflict.

That the above factors have an influence on the occurrence of psychological illness there can be little doubt; but probably a rather more significant and important factor is the nature of the prevailing parental attitudes towards the infant, forming as they do the psychological environment of the latter. The Freudians place much emphasis on the effect on character and personality of early upbringing in such matters as control of urination and defaecation, breast-feeding and opportunity for the expression of early aggressiveness. The work of psychoanalytically orientated anthropologists in interpreting the character-structure of various peoples is as interesting as it is important; such observations have been made on the Chinese by Weston La Barre (41).

In advanced societies it has been pointed out that the stability of inter-parental and parent-child relationships are a more important factor in maintaining mental health than is economic well-being. This is the conclusion of W. L. Neustatter after studying fifty poor families in London (42, p. 37, f.), although some American work appears to show that mental disease is definitely related to poverty (e.g. 43). There are many fallacies in statistical studies of the latter kind, but it seems true, on theoretical ground, that wealth must help to relieve conflict that is not strictly intra-psychic, since it enables one to satisfy one's needs, and execute one's pleasures.

An important aspect of the problem of proneness to conflict is the nature of the personality of the average individual in different societies. The "previous personality" determines not only the liability to neurotic or psychotic breakdown, but also the nature of the psychiatric reaction that ensues when disease sets in. Little or nothing is known of the relation of the prepsychotic personality to mental disease in cultures other than the Euro-American, but it appears that among Chinese schizophrenics the schizothymic type of temperament, identified by means of Kretschmer's self-rating scale, is common, as is the case with Western schizophrenics (35). In regard to the milder psychoneurotic complaints and personality inadequacies in northern Chinese, these have been the subject of study by B. Dai, who analysed the case histories of 2,400 Peking patients, and concluded that such abnormalities arose on a basis of conflict between the immediate social environment and the personality organization, which had been largely moulded by the individual's conception of himself in early life (44; also 45). In this connection we might also note

the approach of L. K. Tao, who attempts to relate such Chinese traits as stubbornness, dependence, lack of power of organization, and "suppression of the personality" to the peculiar stability and influence of the family institution in China (46). We may disagree with his delineation of Chinese character, but his method of analysis is not necessarily a sterile one. The structure of the family, the attitudes of parents to children, and the child's conception of his own self are inextricably mixed.

Several workers have obtained interesting results by making comparative studies of the incidence of neuroticism, in the sense of the frequency of occurrence of neurotic traits, in Chinese and Americans. Making use of Thurstone's Neurotic Inventory, S. K. Chou and C. Y. Mi (47) found that Chinese students were "more neurotic" than American students. A similar conclusion was arrived at by E. Shen, using the Bernreuter Personality Inventory (48). These results can only be of suggestive value, since traits considered neurotic or deviant in America may not be so regarded in China, and, moreover, in translating the inventories, changes in nuance and emphasis might have been introduced. However, T. Pai *et al.* (49) have shown by the criterion of internal consistency that the most diagnostic items in the Thurstone inventory are the same for both Chinese and Americans, thus indicating that it may be useful among the former. Even if the Chinese show a higher neurotic score, it may mean, not that the race or society is less healthy, but that the lack of psychiatric services allow more individuals to remain neurotic than need be.

CONCLUSION.

It clearly emerges from the extension of the psychiatrist's interest to cultures other than his own that there are basic pathological processes to be found in insanity everywhere; processes such as the fragmentation and regression in schizophrenia, to be found in many aspects of the patient's thought and behaviour; the primary changes in mood and in tempo of psychophysiological functioning of the affective reactions; and the psychological and physiological defects and deficiencies of the organic reactions. These are seen everywhere, but the detailed symptomatology of these broad syndromes may vary from one culture to another, reflecting as they do prevailing beliefs, customs, interests and conflicts.

We discern, on turning our attention to the psychoneuroses, all the complexities of the interaction of the individual with his environment. Personality is shaped by cultural environment, and in each culture one or more types of personality may be allowed freer and more healthy expression. Cultures vary in the amount of latitude they allow for change from one sex role to another, and the same applies to roles identified by age, occupation or class. Moreover, there are great variations in the opportunities allowed for the satisfaction of fundamental drives. Man is to a remarkable extent pliable, and "human nature" is not the clear-cut and easily delineated entity it is commonly thought to be.

We obtain a clearer view of the nature of abnormality, and see how much it is dependent on cultural standards. The forms of behaviour in Euro-

American cultures may be conveniently used for comparison with behaviour elsewhere in order to enlarge our understanding of them all, but they are neither necessarily the commonest nor the most healthy, and they do not possess the finality that might come, for instance, from basically biological norms.

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LOSS OF WRITTEN LANGUAGE DUE TO DISSOLUTION OF THE PHONETIC STRUCTURE OF THE WORD IN BRAIN ABSCESS.

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WRITTEN language is a complex function ; being built on the spoken word it has to draw on a variety of subsidiary functions which have to be unified in one particular skill. Moreover, the subsidiary functions are not the same for reading and writing ; in reading, visual-gnostic factors are of major importance, in writing, special skill of hand and finger is required.

The mechanism of disorder in written language is relatively simple when as in pure alexia the visual-gnostic is the predominant factor involved or when, as in isolated agraphia, the apractic-constructive factor is mainly operative. More frequently a number of factors is involved, resulting in a combination of agraphia and alexia which is difficult to analyse ; the difficulties are increased when, as so often, a disturbance of the spoken word is superadded.

The disorder of written language as presented in the following case is unusual because these interfering factors are absent ; for the same reason it presented most favourable conditions for analysis and for investigation of the underlying mechanism.

The patient, A. P—, labourer, a single man, aged 22, gave the following history of his illness : In December, 1948, he started to complain of intermittent blurring of vision, headache and vomiting, which lasted a few days. Further attacks occurred until April, 1949, when the condition became worse, the headache more frequent and intense, and he vomited more often ; he then found that he could neither read nor write ; he was unable to read the names of his co-workers in the factory, and unable to read his daily paper apart from the headline (*Daily Mirror*). He was unable to write the simplest word, or his own name. He was then sent by his doctor to hospital, where an X-ray of the skull showed an intracranial gas bubble with fluid level in the right frontal region. As there was some rise in temperature a brain abscess was suspected, and he was transferred on 21 June, 1949, to the Neuro-Surgical Unit, Bristol. There it was found that he had bilateral papilloedema with retinal haemorrhages, slight weakness of the left lower facial muscles and weakness of the left upper limb. It was also noted that he was unable to read or to write, though he could spell written words. On 29 June, 1949, excision of a well encapsuled brain abscess was carried out ; the abscess was about the size of a plum and was situated in the inferior gyrus of the right frontal lobe, extending from its middle to its posterior portion. He was discharged from the unit on 23 July, 1949, and followed up as an out-patient.

His condition remained at first satisfactory and he was able to return to work, but there was no change in the alexia and agraphia. At the end of October he complained of giddiness and had, for the first time, epileptiform fits. When he was examined later he gave the following description of these attacks, which from his first fit in October, 1949, recurred at approximately monthly intervals. He had been told that about the time of the fits he was given to swearing, attacking others and generally noisy behaviour, which lasted up to a week. He had little recollection of what happened during this period. He remembers seeing strange

things—a man, “fair haired and thick set” coming through the window and “frizzy writing” on the windows, also he remembers reading distinctly, “Blinking fool, hurry, come out and come home.” He saw it quite plainly and could read it easily. In one of the fits he thought German soldiers were chasing him with fixed bayonets and he heard voices calling him and shouting at him.

His previous history showed the following data: He is one of twin brothers. He had measles and underwent tonsillectomy in early childhood, otherwise his development was normal. He describes himself prior to his illness as a happy, contented boy. He was bilingual, went to an English school, but at home spoke mainly French. He says that he was two standards retarded at school, was slow to learn, but picked up more on his own after leaving school. He learned reading fluently, wrote with spelling mistakes in more uncommon words, and made similar mistakes when spelling the spoken word. He had on tests usually 10–15 marks out of 20. After he left school he regularly read his daily paper and some weeklies. He occasionally wrote letters to his relatives and friends. When asked about his reading procedure he says that he used to guess the word from two or more letters, usually the first and the last, and from the length of the word. A report from his school teacher states that he was on the dull side, but had no special difficulties in reading, writing or spelling. He was taught by the phonetic method. After he left school he had jobs on a farm, was employed as a storesman for three years, then as a boiler man and builder's labourer. Prior to his operation he had a severe cold with running nose and cough, but he had no aural discharge. Physical examination showed an operation scar running from about the centre of the forehead posteriorly in a half circle across the right frontal region. Neurological examination showed slight weakness of the lower facial muscles, otherwise there was nothing abnormal.

The following are a representative selection of his reactions to numerous investigations:

Writing.—He writes all the letters of the alphabet correctly and without hesitation; only occasionally he has some difficulties with capital letters, when he writes small letters instead. He is unable to write even very common and short words to dictation; he can write his name, but this is the only word which he writes correctly with confidence and consistency. Otherwise he is unable to write even the most common and short words, and it is very rarely that he succeeds, and this only after many attempts. Here are a few examples:—Plum: “pem, pmo, puam.” Stroll: “cng, sm.” Window: “wdo, wp.” Simple: “spe.” Drag: “rde, red, cprug, drug.” His writing is very slow and hesitant; he tries to get the succession of letters by speaking the word, and even when he correctly puts down the first letter (in this he is most often successful), he is not sure whether he is correct or not. He is equally unsuccessful in putting together words from printed letters. However, he copies words as well as letters without mistakes, copying letter by letter. He writes all the single numbers correctly, and composite numbers up to hundreds; from a thousand on he has difficulties with positioning.

Reading.—The reading of letters, printed or written, is perfect. The reading of words is as severely affected as is the writing; he correctly reads the letters singly, but is, as a rule, quite unable to combine them in the word. Examples:—Dark: there was no spontaneous attempt to read; only when prompted to say the nearest he can think of he produces DEAF, then DAFFA and finally DORMITORY. When asked how many letters the word DORMITORY has he says, “It sounds like a short word; it might have 3 letters.” Fellow: after he has spelled it correctly he says, “Has it anything to do with LADY?” then when this was not accepted by the examiner, “Would it not be PRIVATE?” When reminded that the first letter he spelled was an F he says, “It would not be COFFEE?, it sounds like an F,” then, “CLOTH,” adding, “It would not be with F; there is an H in it,” and then he produces “PHOTO,” but adds again “Photo would not be F,” and finally he says, without much confidence, “FOOT.”

His reading of words and sentences, in writing and in print, was tested on many occasions as was his reading procedure and the results were essentially always the same. As a rule he was not able to read even the simplest word “synthetically,” by putting together the letters which he correctly spelled; nor was he able to recognize the visual character of a particular word. When he succeeded, which was very rarely and only after several unsuccessful attempts, he did so by getting the first sound of the word right, sometimes also the last, and making a more or less lucky

guess, but even then he was never quite certain whether his solution was the right one or not.

There was usually little correspondence between the letters spelled out correctly and the response he produced when trying to get at the word as a whole. Even if he knew that the word he had to read started with a particular sound, and even if he repeated it while trying to form the word, he did not necessarily produce a word with this initial sound; the sound might have been in any part of the word or altogether missing. It did not make any difference whether the words were presented to him in writing or in print. The results were the same, whether he had to read in English or in French, whether it was meaningful for him or not.

Spelling.—The same inability, the same complete disorganization of the word as to its parts became manifest as in his writing attempts. Examples:—WINDOW: H—E; does not know how to carry on. When asked what is the first letter he says S, but is not certain and spells then F—H. CAR: K—H—S—. CAR (repeated) R—H—H—S. FLOOR: F—O—R—N—. DISH: Repeated several times "dish," then D, again probing "dish" D—E—S—. CROWD: O—R. CROWD: S—O—R—. CROWD: S—O—F—O—; tries by saying "crowd;" S— then he starts again C—A—T. PEN: P—E; says "pen" and adds an N.

As with writing and reading, he scores most often in the initial letter. It is exceptional for him to spell a word without grave mistakes; there is usually not only a displacement of sounds, but insertion of letters not contained in the word, so that the word spelled by him has no resemblance to the spoken word. The number of sounds he spells usually does not agree with the number of sounds in the actual word.

He is also incapable of naming even the simplest word when it is spelled out for him.

Various Other Tests to Ascertain the Patient's Capacity to Differentiate the Written and the Spoken Word.

Partitioning of a word into its syllables: After he has been instructed he sometimes gives correct answers, but more often he fails. When two or more words are presented to him orally he is usually quite unable to say with any certainty which is the longer or which the shorter. Nor is he able to say of how many letters or sounds a particular word consists; only occasionally he may give the correct number. When given the same tests in writing his answers are correct.

When a number of written words is presented to him and he has to pick one particular named word he gives the correct answer in about 75 per cent. of trials; the results are poorer when the choice is between similar words than when between words of different lengths and sounds. He is usually guided by the first and last letter, and is more successful with some initials than with others; as further tests show, there are certain initial sounds which he is, as a rule, able to pick out correctly. Occasionally he makes his choice from other letters, as when he recognizes "traffic" from the double "f" in it. The scoring in these tests compared with that in other related tests is fairly high; this might be partly due to the fact that it was applied at a late stage of his examination when he had been subjected to a great number of similar tests connected with word structure; by that time his results had become generally somewhat better than at the beginning of the examination.

In the next test we wanted to find out whether certain initial or end-sounds of a word stand out more and are perceived with more accuracy than others. Five words of various lengths with each letter of the alphabet as initial and end sounds were presented to the patient orally in mixed order. The results were checked over a number of sessions. With the initials he was regularly and unhesitatingly correct only with the "k," "f," and "g" sounds. Next in order came the "d" and "t," "b" and "p," "n" and "m," "c" and "s" sounds, but he was usually unable to distinguish between the members of these pairs; he was also not so sure of the correctness of his answers, even when scoring. The last in order were the vowels, with which he was rarely successful; instead of the vowel he named a consonant which was not necessarily contained in the particular word presented. With successive testing his results showed some improvement. It made no difference if the words presented were English or French, or in a foreign language. For the same

sound the scoring was higher in short than in long words. As for the end-sounds, the same relation between the various sounds in scoring was found as with the initials; but the results were, as a whole, much poorer, and he was much more hesitant.

He failed in analysing two consonant sounds, for instance, "dr" or "pr" and sounds similarly composed. In spite of repeated explanation he failed to name words of a similar sound, or words which rhymed with one or more particular words presented; thus when asked to name a word similar in sound to the word "port" he produces: Jar—Bole—Putty—Potty—, or when asked to give a rhyme to the word "send" the following were his answers: Soil—Sound—Salt—, adding, "It sounds the same, but it does not rhyme." In these tests he often produces words of the same conceptual category instead of sound associations.

In a further test he was asked to form as many words as possible with a given initial. It took him a long time, and except for a few correct responses most of his answers were out of the way. His most common errors were to put the initial sound in any part of the word formed by him. Then, as in the previous test, the same deflection from sound to conceptual categories occurred frequently. Examples: —Letter L: "WELL—ALICE—HELL." S: "S—S—WATCH, —NO—WESTERN—MACHINE." I: "I AM GOING, I SEE—that is E." P: "PALER—WATCH—PENCIL—TEA—NO, it is not P—PORRIDGE—PEN—PAPER." T: "TAPERY—TEA—SUPPER—POINT— is P PRINT— is P—TEARING—STAIRS— it is S—GLASS." He is slightly more successful when he is asked to form from two initials. DA: "DANCE—BON—has a B—DUFFER—TOBACCO—DOOR—, that is G." DR: "DRIZZLING—DRILL—COMPRESSION—DRILLING MACHINE—AB/BORER MACHINE—DRILLING—DAZZLING—EXERCISE—TRYING—," MA: "MAMMA—MOTHER—MAMON—PAPA— it would not be any good." PL: "BELL—PILLOW—PAL—PUZZLE—NO." LO: "LOWRY—LOADING—LOW—LOAF—LOW BUILDING—LOW VAN—LOW—GLOBE—GLOWING." RE: "REFLECT—RECEIVE—RECALL—."

When asked to name the sounds contained in a particular word irrespective of their place in the word he was very uncertain and made many errors. Examples: DRAG: "Sound of an R—, sound of a D—, R is first. Is an H in it?—I don't know." STROLL: "C—F—CR—AS—; is AS in it? Is there a letter after the C? F?—C—S—R—G—."

Conversational speech.—His conversational speech was fluent and he expressed himself well. His comprehension was unimpaired; he could reproduce a small story with most of the details. The naming of concrete objects and of pictures of objects was prompt and without hesitation. His vocabulary was not very rich, but it corresponded to his general intellectual level, which was according to the Wechsler test in the dull normal category, with little difference between the vocabulary and the performance scores. His pronunciation was correct. He discovered grammatical errors, and corrected them when they were intentionally made to test him. This applied for the English language. Comprehension and conversation in French seemed to be unimpaired, though more detailed testing was not carried out.

He recognized popular tunes and could produce them correctly. He could easily and correctly tap out a variety of rhythms.

Apraxia was absent both with objects and with expressive movements. His body orientation was unimpaired. He had no constructive difficulties; drawing from memory and copying were both adequate. Neither were there any disorders in the optic-gnostic sphere; he recognized pictures of objects and situation in all details. He was efficient and accurate in jig-saw puzzles, and he was satisfactory in similar tasks when he had to draw or to construct a whole from parts. He was also within the normal range in the picture completion tests. In Weigl's grouping test he proved to be rigid, and could not shift from the colour to shape.

His arithmetic was very poor; in writing he could do additions well, subtractions with mistakes, but no multiplications or divisions; he was, however, very poor at arithmetic at school and had no practice since; it seems doubtful therefore if a loss attributable to his brain lesion had occurred. His memory for past events and for recent events was quite adequate, as was his immediate retention. On the Wechsler test he had an I.Q. of 86; comparing the Hold with the Don't-Hold there was a loss of 17.5 per cent.

During the period of two months in which intensive testing was carried out there was progressive slight improvement in his defects. Therefore, some tests which were first given at a later date showed somewhat better results than similar

tests given earlier, but the defects in spelling, reading and writing remained very severe during the two months after his discharge from hospital.

Electro-encephalograms were taken on several occasions. The first record showed:—Delta: Persistent focal activity of moderate to high potential at 2 cps in the right frontal region. Theta: Bursts of low-moderate potential at 4–5 cps originating in the right frontal region and spreading back to the right temporo-occipital region, appearing diffusely on the left. Alpha: Low moderate potential, symmetrical, not responsive to physical stimuli at 9–10 cps. Hyperpnoea increased the theta both in amount and in amplitude. Photic stimuli produced a normal response. In successive records the delta activity was less prominent and spread more over the whole of the right cortex.

During his stay in the hospital one major fit was observed; it was reported that he curled up like a ball and turned over on the floor, sustaining an abrasion and some swelling of the nose. He had no recollection of the fit. There was no post-epileptic confusion of any duration.

He was, during the period of hospital observation, always mentally clear, but somewhat restless, and it was difficult to make him follow the rules.

SUMMARY OF THE CASE HISTORY.

The patient, a twenty-two-year-old, right-handed man, whose illness started with intermittent headache and vomiting, found four months later that he could neither read nor write. Before his illness he was a regular and fluent reader of journals and newspapers, but had no great practice in writing, which was rather laborious. A few months after the loss of written language a brain abscess the size of a plum was discovered in the middle and posterior portion of the right lower frontal lobe. The abscess was subsequently excised along with some neighbouring brain tissue. No improvement of his reading and writing capacity occurred after the operation. Three months afterwards he had his first epileptic fit, and since then seizures have occurred at irregular intervals during the period of observation. They were of psychomotor character; during these attacks he had visual hallucinations, some of which consisted of written sentences. Throughout the course of his illness there was no indication of aphasia or visual-gnostic disorder. The disturbance in written language was still very severe more than a year after the operation. There was only very little tendency to restitution at the time the present investigations ended. His agraphia and alexia were purely verbal, and he had no difficulty in reading and writing letters. It was found on numerous tests that there was a complete disorganization of the phonetic structure of the word.

COMMENT.

The special subject of investigation in this case was the disorder of written language which occurred as an early symptom of a brain abscess. The entire complex of writing, reading and spelling was involved exclusively and with the same severity; the spoken word was left intact. Our patient was able to write letters singly without mistake and hesitation and to copy words correctly letter by letter, but he was quite incapable of writing words spontaneously and to dictation; when he tried, he usually produced a sequence of letters which had no relation to the word he was asked to write. The only exception was his name, which he invariably wrote correctly. Similarly he could read all the letters of the alphabet singly without mistake and spell out the written

word letter by letter correctly, but was at a complete loss when he tried to read the word as a whole or when he attempted to put the word together from the letters. Once more the only exception was his name. There was the same severe disorder in spelling as in reading and writing. Detailed examination showed that he was neither able to give the correct succession of the sounds of a word, nor could he say of what sound elements a particular word consisted. On many occasions he was unable to name the initial or the end sounds of a particular word. He could not say of how many syllables a word consisted, nor whether a word was long or short, or which of two words was longer and which shorter. He was unable to form words of similar sound or to rhyme, and he had great difficulty in forming words from an initial sound.

There was, therefore, a severe disturbance of the phonetic details of the word, and the spoken word was almost completely disorganized in its phonetic structure. The patient's inability to spell is a natural expression of this phonetic disorganization of the word and needs no further explanation. His verbal agraphia, characterized by failure to set the correct succession of letters into writing, is also a consequence of the phonetic defect if we assume that the patient was in the habit of spelling out the word when writing, and if we assume that he had not developed a purely visual picture of the word in writing; the latter seems improbable considering that he had always been a rather poor and laborious writer. The alexia, however, is not easily explained from the phonetic defect.

Our patient was taught reading by the spelling method; even so, it can be assumed that he had, with growing skill, developed a visual scheme (Piaget, 1948) of the written word and should therefore have recognized familiar words *ideo-visually*. Though reading may become largely a visual-gnostic function independent of the spoken word, it is as a rule not entirely independent of it. In some way speech articulation or phonetic elements participate and permeate the reading act. It is, therefore, not surprising that disorders of speech interfere as a rule with written language, including reading. This is so commonly the case, despite some exceptions, that the presence of alexia along with agraphia is considered to be one of the most valid signs of a disturbance in internal language. The visual word scheme is thus usually lost when the internal word, the kinaesthetic or the phonetic formula of the word, becomes unavailable. In our case there was, however, no aphasic disturbance, and the word, when spoken, was kinaesthetically and phonetically intact. Our patient's alexia seems to be, therefore, of an order different from that in aphasics.

So far as the alexia is concerned there is a great resemblance to pure word-blindness which is, as generally accepted, due mainly to an *ideo-visual* defect. There is the same inability to read the most simple words, and whilst the spelling out of the written word letter by letter may be undisturbed, the patients are, as in our case, quite incapable of putting the letters together to form the word and quite incapable of reading the word as a whole. In cases of pure word-blindness, spelling and writing are, if at all, only involved to a minor degree. One of the most outstanding features of our case, however, is that the same severe disturbance exists in all those functions which form part of written language. Moreover, the *ideo-visual* disturbance which frequently

accompanies word-blindness in some phase of its course is, in our case, completely absent.

In some respects our patient is comparable to an illiterate ; but there is this difference : that those faculties which are essential for written language had been lost in our case, whilst they are potentially present in the illiterate. Much closer functionally is the relation between our patient's disturbance and congenital word-blindness. This condition occurs in children who, with well developed speech and often very good intelligence, are unable to read or have very great difficulties in learning to read. It was termed word-blindness, as it appeared to be the congenital replica of pure word-blindness which had been previously described in focal lesions of the brain in adults. Earlier descriptions of such cases suggested that the alexia was indeed the essential feature in the congenital as well as in the acquired form of word-blindness. However, detailed investigations carried out more recently have shown that the difficulties of these children are not confined to reading ; in a great number of cases they were as marked in spelling and writing. This and more detailed analysis of the cases led to a revision of the opinion previously held. A review of most of the modern work on this subject has been given by Solms (1948). The approach and the results of different authors vary, and a generally accepted solution has not been found. Ombredané (1937), in considering mainly reading difficulties, distinguishes a phase of exploration and one of elaboration during the reading act ; in congenital wordblindness both of these are, in the opinion of Ombredané, pathologically slowed down. Frank (1936), Rombach and Kern (1937) and Pflugfelder (1948) speak of the solidity of the optic structure of the word and weakness of analysing it. Ley (1929) thinks there is mainly a failure to synthesize, and Thiele (1938) emphasizes the inability to analyse and to synthesize the word. Orton (1937), who has a physiological approach, is of the opinion that it is interference by the minor hemisphere which causes the difficulties. Of special interest with regard to our own case are the observations of Bachman (1927) and Hermann and Voldby (1947), who speak of a confusion of letters in their series of children and a patient of Ley (1931), who declared that he did not hear the letters in the word and could, therefore, neither spell nor write.

The case descriptions as well as the differing opinions of the various authors suggest that the pattern of what is termed congenital word-blindness is not uniform, but there is a group of these children in whom the difficulties are almost identical with those of our patient. As in our case, no disorder in the optic-gnostic function can be found ; spelling, reading and writing are equally severely involved ; writing and reading of single letters is almost undisturbed ; the spelling of the written word does not offer any difficulties, and letters which are phonetically akin are often mixed up in spelling and writing. The phonetic differentiation of the word, either written or spoken, seems to be lacking in the same way as we found it in our observation. There is, therefore, the same problem which faced us in our investigation, namely, the incapacity to read the word *ideo-visually*, though its phonetic structure does not seem to be directly involved in this procedure.

It appears that this problem cannot be solved as long as we measure *ideo-*

visual reading procedure by general gnostic rules; according to these the written word has its particular visual character, and the identification of this character is a skill which can be acquired provided the visual-gnostic function is intact. These visual-gnostic rules may be valid as long as the language is intact. In aphasia, as mentioned before, ideo-visual reading is not maintained and alexia is the rule. The way in which reading can be involved by a phonetic disorganization of the word without aphasia is indicated by the description which our patient volunteered. Though he was taught reading by spelling, later, according to his own information, he would, when reading, pick out one or two letters of the word and guess at the word. It is interesting to note that his description conforms with the perceptual procedure found in tachistoscopic exposure, where the perception of one or two letters and the length of the word ensures a correct reading. In such reading procedure the word formation takes place from details perceived by a non-perceptual process. The "closure" to the Gestalt might, under these circumstances, be a visual process identical with that which, under other conditions, occurs on non-verbal objects. Such process was not blocked in our patient by any lack of visual imagery, as his drawing shows. It is, however, not less likely that at this procedure a transposition into the phonetic sphere takes place, that the visual elements perceived evoke the corresponding sound elements and that the word is thus completed phonetically. This is what probably happened in our patient. There will be then no difficulty in explaining our patient's failure to read, because we have seen that he is unable to guess at the word from single sounds presented and unable to form a word from phonetic elements. It is, therefore, significant, and seems to confirm the observation in our case, that children with congenital word-blindness are, when reading, unable to by-pass spelling, and in systematic training the ideo-visual method is, if anything, less successful than the spelling method (Hinshelwood, 1917; Hall, 1947, *et al.*) This means, in our opinion, that they are unable to learn to identify the visual character of the word without first getting hold of the phonetic structure; they are bound to fail because the phonetic structure of the word is absent.

The mechanism involved can be summarized as follows: When the word is perceived ideo-visually, this visual whole is not without structure, as described by our patient and as demonstrated in tachistoscopic examination. Some details will always stand out and form part of the specific character of the whole, and it seems that these details cannot, at least in some persons, "close" to the visual Gestalt without phonetic support.

The finding that the spoken word should be intact whilst it lacks structure is not as paradoxical as it might appear. There is a transitory stage during normal development of language when words are perceived in a "syncretistic" (Claparède, 1907) way incompletely structured and as a general scheme without details. It is only at a later stage that a more complete structure and organization of the word is attained, but this is not an essential part of spoken language. In conversational speech the emphasis is on sentence formation and the scheme is propositional; consequently the word as a whole becomes part of the total propositional structure. It functions in its general scheme and phonetic details are of minor significance. When, on the other hand, the

word has to be used in written language the propositional scheme is replaced by the word scheme. The word has now become a self-contained unit which requires organization ; it is organized as to its phonetic details, and these form the elements of the word in the same way as the word as a phonetic whole is part of the organization of the sentence.

Functionally the word has therefore two distinctive qualities, a propositional and an exclusive word quality ; one is linked up with the spoken word, the other with the written language. As aphasia is primarily a disturbance of the spoken word it is of interest to compare the agraphia and alexia in aphasia with the disorder of written language in our case. The character of agraphia and alexia in aphasia may vary considerably, but we can, for our purpose, distinguish two groups ; in one there is a close connection between the confusion of the spoken and that of the written word. In the other group no such relation can be discovered. In the first group of cases the reading and writing may proceed fluently, and the mistakes made are very nearly the same as those when the word is spoken. (Read and written paraphasias.) The patients have, therefore, retained the ability to express the spoken word, altered as it is, in reading and writing ; to do this its detailed structure must necessarily be available ; the paraphasic word must be well organized as to its particular sounds. Therefore, the disorder is not a defect of word structure ; it is not the details of the word that are primarily disorganized, but the word as a whole, the Gestalt quality of the word. The word scheme has become unprecise, uncertain and unstable. This is then just the opposite to what we found in our observation. While in our case the structure of the word, the special word quality has been lost, we have in these aphasics a disturbance of the Gestalt or the propositional quality of the word. There is, accordingly, in our case an exclusive loss of written language, whilst in this group of aphasics the word, as it is spoken, can be expressed in the written language ; thus the agraphia and alexia of these aphasic patients is not a disorder *sui generis*, but reflects only the altered scheme of the spoken word.

The paraphasic reading in these aphasics is also of interest in view of the reading mechanism previously discussed ; the parallelism between written and spoken word shows that the word formation at reading is not determined by the visual character of the word, but by its phonetic structure.

The group of aphasia discussed is relatively easy to analyse with regard to the relation between the spoken and written word. In the other group of aphasics the alexia and agraphia are usually more complex ; as indicated by the inability to write and read letters, there are often, apart from aphasic, apractic-constructive and visual agnostic factors effective. One or the other of these factors may be prevalent, since in some cases reading, in other cases writing, is predominantly involved. This is not to say that aphasia leaves the structure of the word necessarily intact ; phonetic disintegration in motor aphasia has been recently mentioned by Alajouanine and Mozziconacci (1947), but the complexity of the picture usually makes it difficult to isolate a possible structural disorder of the word. This question could be decided more easily in cases where the restitution of the spoken word precedes that of written language or where the aphasic disturbance is only slight. Such a case was first

described by Déjerine (1891) as a separate syndrome of agraphia and alexia, and a number of similar cases (Serieux, 1892; Stier, 1917; Hermann and Pötzl, 1926; Nielson, 1945; *et al.*) were subsequently reported. In these cases the agraphia was usually predominant and involved the writing of letters as well as that of words. From this it appears that the character of the disturbance is quite different from that found in our case. An exception is a clinical observation by Brandt (1928), in which, after a transient aphasia, agraphia and alexia persisted of a character similar to that in our case; reading, writing and spelling were equally and almost exclusively involved. This observation indicates that an exclusive disorder of written language of the same character as here described can occur as a residual syndrome in aphasia.

Localization.—Since Déjerine's description of agraphia and alexia in connection with a lesion in the cortex of the left angular gyrus, this part of the brain has been generally considered as significant for this syndrome, although anatomical reports have been very rare. No lesion in any other part of the brain is claimed to produce the combination of isolated agraphia with alexia. In our case an encapsulated brain abscess was demonstrated in the triangular-opercular portion of the right hemisphere in a man who was indubitably right-handed. This is an unusual site with regard to the clinical picture. However, the focal lesion need not necessarily be the cause of the syndrome; it may well be due to a general cortical dysfunction. We have so far considered the disorder from a perceptual angle, but seen conceptually our patient's difficulties in spelling and writing can be regarded as an inability to analyse the spoken word, and his difficulties in reading to an inability to synthesize the single letters to the word—a point already made by Thiele regarding cases of congenital wordblindness. If such defect in analysis and synthesis would prove to be general, then the disorder of written language could be regarded as an expression of a general lowering of cortical function; but, as in congenital word-blindness, there is little evidence for such an assumption. Our patient's general intellectual level has not dropped to any extent, and his capacity to analyse and synthesize was found intact on performances other than written language. We might also consider whether the patient's low school standard and rather low level of skill in written language were not factors which made the written language more vulnerable than other functions. The effects of individual ability and acquired degree of automatism upon the clinical picture in brain lesions have been frequently discussed in the literature. Though there is some evidence that these factors may be of importance for particular disorders within a functional complex, it is unlikely that a special function, such as written language, should be singled out by a general process, whilst other functions showing a skill and automatization of about the same level should be spared.

It seems, therefore, that we have to attempt to explain the disorder by the local lesion found in our patient. In relating a disorder of written language to the focal lesion the following has to be considered. There are, as pointed out, aphasias in which the spoken word, though transformed, is well constructed, and the capacity to organize the word as to its sounds is preserved; written language is thus intact so far as it represents the true copy of the spoken word.

The anatomical lesions in these cases can be found in any portion of the speech area of the dominant hemisphere, though specially in the posterior parts, i.e., in the temporal region. As it can hardly be assumed that the damaged area would exclusively maintain the written word, one of the most elaborate functions of the language, these findings would therefore suggest that there is not only a functional but also an anatomical separation of the two functions, the spoken and the written word. There is good reason to believe that under these circumstances written language might be subserved by the corresponding area of the non-dominant hemisphere, an area which seems to be capable of taking over some of the functions of language when the superior hemisphere is out of action, and which is, in the opinion of some authors, responsible for special functions of language. Its significance for written language has been stressed by Orton. In our case an anatomical destruction was found in the right frontal lesion; epileptic seizures of psychomotor character with visual hallucinations would indicate that the temporal lobe was also involved. Thus a large portion of the cortex of the right hemisphere corresponding to the speech area on the left side has probably been damaged. When we accept the opinion that both hemispheres control language, we have to assume that in our case those functions of language which are the basis of the written word were dependent upon the right hemisphere, whilst the left dominated the spoken word. It is perhaps not without significance that the structural dissolution of the word which we found in our case is also a spatial disorganization, as the patient is unable to put the elements of a particular word into the correct spatial order. We know from clinical experience that spatial organization is largely dependent upon the non-dominant hemisphere.

As to the rest of the clinical picture, the patient's visual hallucinations during post-epileptic excitement are specially worth mentioning. Among the visions he experienced were hallucinations of written sentences which, according to his descriptions, were projected on the window and were very vivid, distinct and real; he had no difficulty in reading them, and could still recollect one of the sentences. His word-blindness did not therefore exist in his hallucinations. This seems to show that such experiences are not necessarily derived from perceptive or ideatory sources, because our patient was unable to perceive or visualize the written word.

SUMMARY.

In a twenty-two-year-old, right-handed man, one of the first signs of an abscess in the right inferior frontal lobe was loss of ability to read and to write.

It was found on examination that the patient was unable to spell, read and write the simplest words, with the exception of his name, whilst he could read and write single letters and spell the written word. It could be demonstrated on a variety of tests that the word was completely disorganized as to its phonetic structure. There was no disturbance of the spoken word, nor was there any visual-gnostic disorder.

This syndrome was discussed first in relation to the almost identical defect in a certain group of congenital wordblindness. In both conditions the verbal

alexia seemed to be the disturbance most difficult to explain ; it was suggested that in the reading act visual perceptions were carried into the phonetic sphere so as to complete the word Gestalt ; as the phonetic structure of the word is not available, reading is not possible.

A distinction was made functionally between the word when used in written language and when used as part of the spoken sentence. In written language structural detail of the word is a requisite (special word quality). When the word forms part of the sentence it functions as a whole and structural details are not required (propositional quality). In the case here described there was a disorder of the special word quality only ; therefore the spoken word was intact. In aphasia, mainly a propositional disorder, the word as to its whole may be disorganized without involving the structure of the word ; under these circumstances the written word is a true copy of the spoken paraphasias.

No evidence could be found for a general lowering of cortical function to explain the disorder in written language. The local destruction was in the right lower frontal lobe ; epileptiform seizures of psychomotor character indicated that there was also involvement of the temporal region. A large part of that area which represents, on the corresponding left side, the speech area was therefore probably damaged. The otherwise inferior hemisphere seemed thus to have been dominant for those special functions of language which are the prerequisites of the written word. Such anatomical separation of the two functions, that of the spoken word and that of the language abilities necessary for the written word, does not seem to be exceptional ; it can also be demonstrated in aphasics.

The investigation was carried out at the Bristol Mental Hospitals.

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PERMEABILITY OF THE BLOOD-BRAIN BARRIER TO PENICILLIN IN CASES OF PARENCHYMATOUS NEUROSYPHILIS.

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SINCE the introduction of penicillin into therapeutics the important question of the penetration of the blood-brain barrier by the antibiotic in infections of the nervous system has cropped up. In vital staining experiments Goldman (1913) observed that the acid semi-colloidal dye, trypan blue, which makes its way from the blood into the tissues, is unable to penetrate into the central nervous system. When the dye was injected into the cerebrospinal fluid it passed without difficulty into the brain substance. These observations were later verified by other investigators and have been verified for other substances (dyes, drugs, toxins, etc.).

There exists a special mechanism which regulates the exchange of substances between the blood and the brain. Spatz (1924, 1931), Friedmann and Elkeles (1934), and Broman (1940), have proved that the inhibitory effect is localized to the walls of the cerebral vessels, and that it is connected with the permeability of these vessels. There are two routes by which substances pass from the blood to the brain :

1. By way of the cerebral vessels, i.e. directly.
2. By way of the cerebrospinal fluid, i.e. indirectly.

The former is the more important and quantitatively dominant one and should be referred to as the blood-brain barrier. The latter should be referred to as the blood-cerebrospinal-fluid barrier, and it is situated at the choroid plexus.

The blood-brain barrier and the blood-cerebrospinal-fluid barrier raise different problems (Broman, 1941).

Friedmann and Elkeles (1934) made a most interesting and important discovery about the dyes and other substances, namely, that the electric charge plays a most important role for their passage into the central nervous system. Electro-negatively charged (i.e. acid) dyes are generally incapable of penetrating the central nervous system by the blood route. They may, however, if the concentration is high, pass into the cerebrospinal fluid to a certain extent and then pass into the brain. Electro-positively charged (i.e. basic) dyes very easily enter into the central nervous system by the blood route, whereas their entrance into the cerebrospinal fluid is small.

Penicillin is an acidic antibiotic, and in this respect it appears to behave

like acid dyes (electro-negatively charged), in only penetrating into the cerebrospinal fluid in small amounts.

Macklin and Macklin (1920), Skoog (1937), and Broman (1938, 1940) have shown by means of intra-vital staining with dyes that, in lesions of the central nervous system the cerebral blood vessels are more permeable.

Sorsby, Wright and Elkeles (1943) found that certain brain tumours in the central nervous system stained with Kiton fast green (which behaves like an acid dye) after it was injected parenterally, whereas normal brain tissue remained unstained.

In neurosyphilis the meninges, the blood vessels and the parenchymatous tissue are affected to a varying degree. In general paralysis of the insane and in tabes dorsalis the parenchymatous involvement is the more severe.

There can be little doubt that the cerebral vessels in parenchymatous neurosyphilis are more permeable to substances in the blood than when no disease of the central nervous system exists.

It has been pointed out by Elkeles (1943) that there seems to be a similarity between the blood-brain barrier and blood-cerebrospinal-fluid barrier regarding their permeability to substances in the blood under certain pathological conditions.

The detection of a chemotherapeutic agent in the cerebrospinal fluid in pathological conditions of the central nervous system would be evidence in favour of the substance having passed the blood-cerebrospinal-fluid barrier, and would also be presumptive evidence in favour of its having passed the blood-brain barrier.

The fact that penicillin cannot be detected in the cerebrospinal fluid, is, of course, no proof that penicillin has not passed the blood-brain barrier to reach the nerve cells of the central nervous system. It is known that cases of parenchymatous neurosyphilis have responded satisfactorily, clinically and serologically, to moderate doses of penicillin, although it could not be demonstrated in the cerebrospinal fluid (Smith, 1947). Presumably penicillin had penetrated into the brain directly in order to influence effectively the pathological process (Smith and de Moraes, 1948). As Moore (1944) points out, "the effectiveness of chemotherapeutic substances does not necessarily depend on the ability of that substance to penetrate into the cerebrospinal fluid. Instead it depends on the basis of penetrability into the diseased brain tissue, i.e. the blood vessels, the meninges and the parenchyma."

When treating patients with neurosyphilis it is well to keep in mind the pathology of the disease. The nervous system is invaded early in the general infection by spirochaetes from the blood stream. Even though the blood-brain barrier prevents direct invasion of the brain and spinal cord except in the foetus in the early months of pregnancy, the organisms pass through the blood-cerebrospinal-fluid barrier (choroid plexus), to enter the ventricles and the subarachnoid space. The ependymal linings of the ventricles and the pia mater throughout the central nervous system are attacked by the spirochaetes; all neurosyphilis seems to begin as a surface infection.

When the parenchyma of the central nervous system is involved, our aim should be to make sure that the penicillin not only gets across the blood-cerebro-

spinal-fluid-barrier into the cerebrospinal fluid, but also gets across the blood-brain barrier to reach the tissues of the nervous system and kill off all spirochaetes.

Eagle and Musselman (1944) have demonstrated, *in vitro*, that spirochaetes are sensitive to relatively low concentrations of penicillin. The tests were carried out on non-pathogenic strains—the so-called Reiter, Kazan, Nichols and Noguchi strains. Therefore it may well be that the pathogenic strains in man require much higher concentrations of penicillin to eradicate them.

Patients with parenchymatous neurosyphilis having penicillin in ordinary standard doses presumably get a maximum concentration in the nervous system quite near to or equal to the relatively low concentrations necessary to destroy the *Tr. pallidum*, but the safety factor may be small.

REVIEW OF THE LITERATURE.

The first report on the distribution of penicillin in the body after it had been administered in different ways was made by Abraham *et al.* (1941). From studies with experimental animals they found that penicillin disappeared rather rapidly from the blood after a single intravenous injection, but that a large percentage of the amount administered was found in the urine. When given subcutaneously the concentration in the blood was less, but a detectable amount was present for a longer period of time than after a single intravenous injection. Tears, pancreatic juice and cerebrospinal fluid had no anti-bacterial activity when penicillin was given intravenously.

Fleming (1943), while treating a case of streptococcal meningitis with 15,000 units intramuscularly every two hours, observed that the cerebrospinal fluid was only bacteriostatic to a dilution of 1 in 2, while the blood serum was bacteriostatic to a dilution of 1 in 4. As the patient was not responding to treatment, penicillin was injected intrathecally with good effect.

The observations of Abraham and his colleagues on experimental animals were extended to human patients by Rammelkamp and Keefer (1943). These workers found that after 10,000 and 20,000 units of penicillin intramuscularly or intravenously, the drug does not pass into the cerebrospinal fluid in detectable amounts.

Herrell (1944) administered 30,000 units of penicillin intravenously in a period of 15 minutes to a patient who had no demonstrable lesion of the central nervous system. He could not detect the drug in cerebrospinal fluid removed 30 and 60 minutes after injection.

In a case convalescent from pneumococcal meningitis, Cairns *et al.* (1944), after 100,000 units of the substance intravenously, were able to demonstrate penicillin in the cerebrospinal fluid in amounts sufficient to inhibit the growth of staphylococci at a dilution of 1 in 2.

Although they were aware that penicillin did not appear in cerebrospinal fluid after moderate doses of the drug intramuscularly, Nelson and Duncan (1945) reported excellent results in 10 cases of syphilitic meningitis treated intramuscularly. They gave 10,000 to 50,000 units of penicillin every three hours, with a total varying from 600,000 to 4,000,000 units of penicillin.

Herrell *et al.* (1944) treated four patients with 100,000 units of penicillin a day by continuous intravenous administration. Two specimens of cerebrospinal fluid were taken from each patient while the treatment was in progress, but no evidence of penicillin activity was found.

Using three-hourly systemic injections of 20,000 to 40,000 units of penicillin by the intramuscular and intravenous route, Rosenberg and Sylvester (1944) found concentrations of 0.03 to 0.05 unit per c.c. in the cerebrospinal fluid in times varying from 60 to 140 minutes.

In three cases of neurosyphilis treated at the Mayo Clinic and reported by Stokes *et al.* (1944) penicillin was not detected in the cerebrospinal fluid after intramuscular injection.

As part of a wider study of the distribution of penicillin in the body, Cooke and Goldring (1945) made observations in 5 infants with acute meningitis. Their ages ranged from 4 to 34 months. All the cases were found to have the drug in the cerebrospinal fluid 15 to 60 minutes after intramuscular injection. These patients received 500 to 5,000 units per kilogram of body weight, doses much larger than were usually given to adults.

In experimental treatment of dementia paralytica, Neymann *et al.* (1945) gave a patient massive doses, up to 1,000,000 units of penicillin dissolved in 1,000 c.c. of a 5 per cent. dextrose solution intravenously during a three-hour period. Specimens of cerebrospinal fluid taken immediately afterwards did not reveal the presence of penicillin. Another patient received a total dose of 3,000,000 units of penicillin intramuscularly during an eight-day period and no penicillin was detected in the cerebrospinal fluid. A second attempt was made to breach the blood C.S.F. barrier by giving the patient 10 c.c. of a 20 per cent. sodium dehydrocholate solution intravenously during the time penicillin was being administered. This drug is credited with increasing the permeability of tissues and capillaries. No penicillin was found in the cerebrospinal fluid. Another patient was treated with artificial fever by the fever cabinet and penicillin. During the first febrile period, 400,000 units of the drug were given by the intravenous drip; during the second, 500,000. In both instances the cerebrospinal fluid showed no trace of penicillin immediately after treatment. Neymann concluded that the barrier could not be breached by these methods.

According to a report by McDermott and Nelson (1945) in patients who had received one or two intramuscular injections of 300,000 to 500,000 units of penicillin, only 0.02 unit per c.c. was found in the spinal fluid three to four hours later.

From observations in the rabbit and in man, Lourie and his colleagues (1945) found that large doses of penicillin must be given before the drug is detected in the cerebrospinal fluid. In a patient with presumably normal membranes of the brain, three injections of 600,000 units of penicillin at hourly intervals had to be given before even slight amounts of the drug could be detected in the cerebrospinal fluid.

Smith *et al.* (1946) treated one case of pneumococcal meningitis with 40,000 units every three hours intramuscularly. A relapse occurred, showing that curative amounts of penicillin did not enter the cerebrospinal fluid.

Schwemlein and his colleagues (1946) reported observations on the penicillin content of the cerebrospinal fluid in patients treated by intravenous penicillin. Their patients were suffering from primary and secondary syphilis. Sodium penicillin was administered by continuous intravenous drip in amounts ranging from 10 to 25,000,000 units during a 24-hour period. The total amount of penicillin was contained in 1,000 c.c. of isotonic saline solution. Penicillin was demonstrated in measurable concentration in the cerebrospinal fluids of 126 patients. 162 patients received these large amounts of penicillin. There were no convulsions or signs of meningeal irritation.

Kaplan *et al.* (1946) treated 12 cases of neurosyphilis: 8 asymptomatic, 2 meningovascular, 1 tabes, and 1 G.P.I. Each had intramuscular penicillin in 30,000 unit doses and malaria. They could not detect penicillin in the cerebrospinal fluid 10-150 minutes after the injection.

Dumoff-Stanley *et al.* (1946) made 16 studies on the absorption of penicillin into the cerebrospinal fluid in 14 patients, during intravenous and intramuscular administration. Penicillin was present in the subarachnoid fluid of 6 patients, 4 of whom had disease of the meninges. No patient with serum concentrations of less than 0.625 unit per ml., and no patient who had penicillin in his blood stream for less than 12 hours obtained concentration in his cerebro-spinal fluid which might be considered therapeutically effective. In a patient convalescent from pneumococcal meningitis I was unable to detect penicillin in the cerebrospinal fluid 30 minutes and 60 minutes after 10,000 units of the drug had been injected intramuscularly.

Redfearn *et al.* (1949) reported that the blood-cerebrospinal fluid barrier in patients with no demonstrable lesions of the central nervous system was permeable to penicillin after intramuscular injection. Large doses of 0.5 mega unit to 1.0 mega unit were given. Ten patients with late parenchymatous neurosyphilis were also studied, and in 9 of the cases penicillin was demonstrated in the cerebrospinal fluid six hours later, following single intramuscular doses of 0.5, 1.0 and 2.0 mega units.

Most workers mentioned above agree that, after intramuscular administration of doses of penicillin commonly used in standard schemes of treatment, penetration of the antibiotic into the cerebrospinal fluid cannot be demonstrated. On the other hand, when large doses are given, some of it penetrates into the cerebrospinal fluid.

SCOPE OF PRESENT STUDY.

Penicillin is being given a prominent place among agents employed in the treatment of neurosyphilis (Thrasher, 1945; Goldman, 1945; Stokes, 1945; Callaway *et al.*, 1945; Gammon *et al.*, 1945; Rose and Solomon, 1947; Heymann, 1947; Reynolds *et al.*, 1946; Worster-Drought, 1947; Lindsay, 1947; Purdon Martin, 1948; Dattner, 1948).

Very little has been written on the use of penicillin alone in general paralysis of the insane and tabes dorsalis. The majority of workers give it with fever or arsenicals or both.

The treatment of a case of parenchymatous neurosyphilis with penicillin is by no means standardized. No hard and fast rules have been laid down with

regard to the optimum dose, the time spacing of injections, the duration of treatment or the route by which the drug is to be given.

According to the literature, when the intramuscular route is chosen the drug must not be given for less than $7\frac{1}{2}$ days, and the total dosage varies from 2 to 10 million units or more.

Some cases of parenchymatous neurosyphilis treated with moderate dosage of penicillin relapsed (Reynolds *et al.*, 1946; Rose and Solomon, 1947). Re-treatment with larger doses gave satisfactory results.

A question arises with regard to these relapses. Did the antibiotic in moderate doses penetrate into the substance of the nervous system in sufficient concentration to have lethal effect on all the spirochaetes?

It is important to know whether penicillin passes into the nervous system in adequate amounts after it is given parenterally. The writer therefore investigated this in 16 patients with parenchymatous neurosyphilis who were having intramuscular penicillin alone in routine treatment. They were classified clinically as follows:

G.P.I., 8 men, 5 women.

Tabo-paresis, 1 man.

Tabes dorsalis, 2 women.

For purposes of description they are divided into:

Groups A and B (low dosage group).

Groups C and D (high dosage group).

BIOLOGICAL ASSAY FOR PENICILLIN.

The tests for the amount of active penicillin in the body fluids in Groups A and B were made by the agar plate method, using *Staphylococcus aureus* as the test organism. The sensitivity of the organism was equal to the one used in the School of Pathology, Oxford, for such determination. In Groups C and D the penicillin estimations were made by using *Bacillus subtilis* as the test organism, as recommended by Randall Price and Welch (1945), according to the reductose method described by Reid and Brewer (1946).

The studies on the penicillin content of the body fluids were in general agreement with those reported by Fleming *et al.* (1944) and others.

RESULTS.

Group A (low dosage).

Four male patients (Cases 1, 2, 3 and 4) with general paralysis of the insane were receiving 20,000 units of an aqueous solution of penicillin three-hourly for $7\frac{1}{2}$ days. On the third day of treatment specimens of cerebrospinal fluid were obtained for assay at 15, 30, 45, 60, 120 and 180 minutes after the early morning intramuscular injection. Two of these patients had specimens of blood and cerebrospinal fluid taken simultaneously.

The qualitative results are indicated in Table I. Table II indicates the serum concentrations of penicillin at the times the cerebrospinal fluids were obtained. No penicillin could be detected by the method used in any of the

cerebrospinal fluids, but penicillin was present in the blood sera for three hours in two of the patients.

TABLE I.—*Group A : Qualitative Results of the Tests for Penicillin in the Blood and Cerebrospinal Fluid of Patients with G.P.I. after Intramuscular Injection of Penicillin.*

Case.	Penicillin.	Specimen.	Time intervals after injection in hours					
			$\frac{1}{4}$	$\frac{1}{2}$	$\frac{3}{4}$	1	2	3
1	20,000 units	Blood	.	.	.	.	.	.
		C.S.F.	—	—	—	—	—	—
2	,, ,,	Blood	.	.	.	.	.	.
		C.S.F.	—	—	—	—	—	—
3	,, ,,	Blood	+	+	+	+	+	+
		C.S.F.	—	—	—	—	—	—
4	,, ,,	Blood	+	+	+	+	+	+
		C.S.F.	—	—	—	—	—	—

TABLE II.—*Group A : Quantitative Results of Determination of Penicillin in the Blood and Cerebrospinal Fluid after 20,000 Units Intramuscularly.*

	Hours after injection.	Serum concentration (units per ml.).	C.S.F. concentration (units per ml.).
Case 3, G.P.I. (male)	$\frac{1}{4}$	335	0
	$\frac{1}{2}$	290	0
	$\frac{3}{4}$	200	0
	1	100	0
	2	100	0
	3	100	0
Case 4, G.P.I. (male)	$\frac{1}{4}$	500	0
	$\frac{1}{2}$	335	0
	$\frac{3}{4}$	250	0
	1	100	0
	2	100	0
	3	100	0

Group B (low dosage).

Three male patients (Cases 5, 6 and 7) with G.P.I. were receiving 50,000 units of an aqueous solution of penicillin intramuscularly 4-hourly for $7\frac{1}{2}$ days. On the third day of treatment at 30, 45, 60, 120, 180 and 240 minutes after the early morning injection, specimens of blood and cerebrospinal fluid were obtained simultaneously.

The qualitative results are indicated in Table III. Table IV indicates the serum concentrations of penicillin at the time the specimens of cerebrospinal fluid were obtained.

No penicillin could be detected in any of the cerebrospinal fluids, but penicillin was found in the blood sera for 4 hours after injection.

TABLE III.—*Group B: Qualitative Results of the Tests for Penicillin in the Blood and Cerebrospinal Fluid after Intramuscular Injection of Penicillin in cases of G.P.I.*

Case.	Penicillin.	Specimen.	Intervals in hours after injection.					
			$\frac{1}{2}$	$\frac{3}{4}$	1	2	3	4
5	50,000 units	Blood	+	+	+	+	+	+
		C.S.F.	—	—	—	—	—	—
6	,, ,,	Blood	+	+	+	+	+	+
		C.S.F.	—	—	—	—	—	—
7	,, ,,	Blood	+	+	+	+	+	+
		C.S.F.	—	—	—	—	—	—

TABLE IV.—*Group B: Quantitative Results of Determination of Penicillin in the Blood and Cerebrospinal Fluid after 50,000 Units Intramuscularly.*

	Hours after injection.	Serum concentration (units per ml.).	C.S.F. concentration (units per ml.).
Case 5, G.P.I. (male)	$\frac{1}{2}$	860	0
	$\frac{3}{4}$	720	0
	1	680	0
	2	200	0
	3	100	0
	4	100	0
Case 6, G.P.I. (male)	$\frac{1}{2}$	720	0
	$\frac{3}{4}$	600	0
	1	400	0
	2	100	0
	3	100	0
	4	100	0
Case 7, G.P.I. (male)	$\frac{1}{2}$	720	0
	$\frac{3}{4}$	600	0
	1	340	0
	2	100	0
	3	100	0
	4	100	0

Observations made on the patients in the low dosage groups included examinations of the blood and cerebrospinal fluid at 3-monthly intervals in addition to full physical and neurological assessment. One patient relapsed 9 months after completion of treatment. The cells and the total protein in the cerebrospinal fluid began to increase and the W.R. remained positive.

This patient had received a course of 50,000 units 4-hourly for $7\frac{1}{2}$ days, followed one month later by a similar course. It was thought that perhaps not enough penicillin had been given. During the first course the antibiotic had not been detected in the cerebrospinal fluid, although an appreciable amount had been found in the blood. It was argued that as penicillin had not

penetrated the blood-cerebrospinal fluid barrier in detectable amounts, the drug had not penetrated the blood-brain barrier to the diseased parenchyma of the brain in adequate amounts.

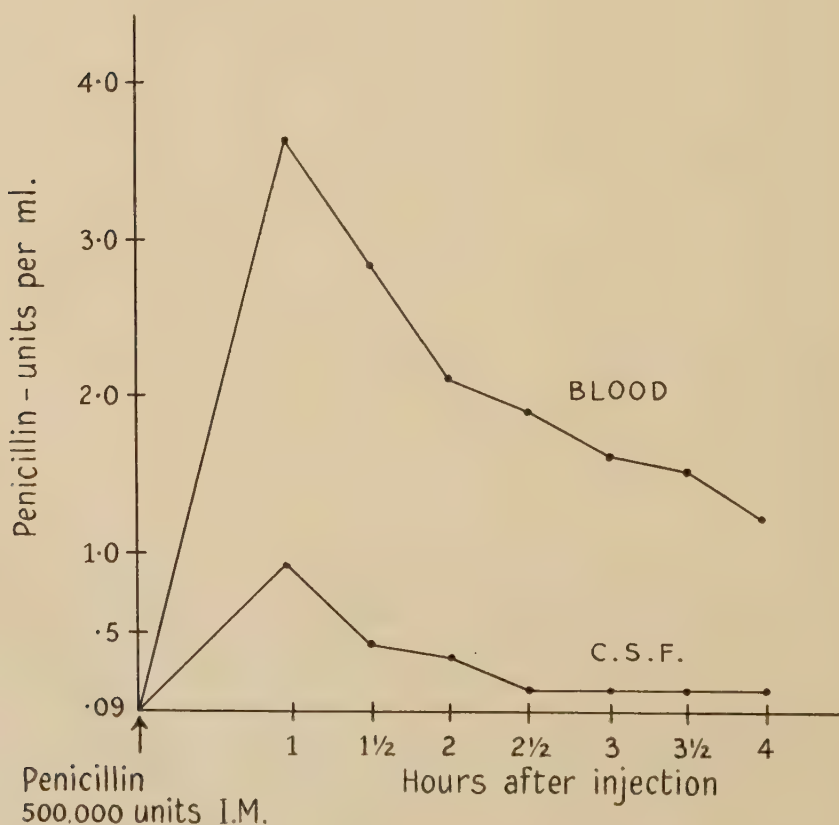
It was decided to find out what dose of penicillin should be given intramuscularly to patients with parenchymatous neurosyphilis in order to demonstrate it in the cerebrospinal fluid. A patient with G.P.I. was given one dose of 100,000 units, but no penicillin was found in the cerebrospinal fluid at intervals afterwards. The same patient was then given 200,000 units. No penicillin was detected in the cerebrospinal fluid.

The following investigations were then undertaken :

Group C (high dosage).

Four women (Cases 8, 9, 10 and 11), 3 with G.P.I. and 1 with tabes dorsalis were treated by a large dosage schedule. In order to protect the patients from a Herxheimer reaction, treatment was commenced with small doses as follows :

1st day	20,000 units	3-hourly	for 8 doses.
2nd "	50,000	" 3	" 8 "
3rd "	100,000	" 3	" 8 "
4th-10th	500,000	" 4	" 42 "



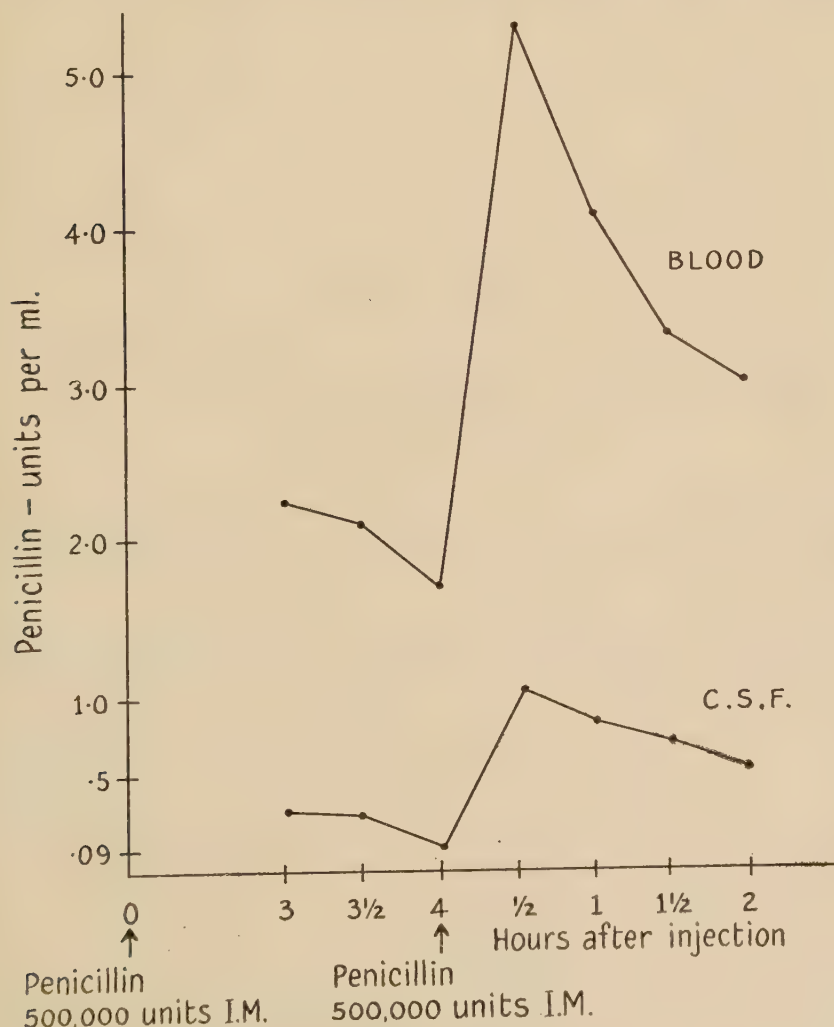
GRAPH 1.—Penicillin levels in body fluids. Case 8, female, aged 47. Diagnosis : General paresis of the insane.

On the 4th day treatment with 500,000 units 4-hourly was commenced. At varying intervals after the morning injection of the first 500,000 units, specimens of blood and cerebrospinal fluid were obtained simultaneously.

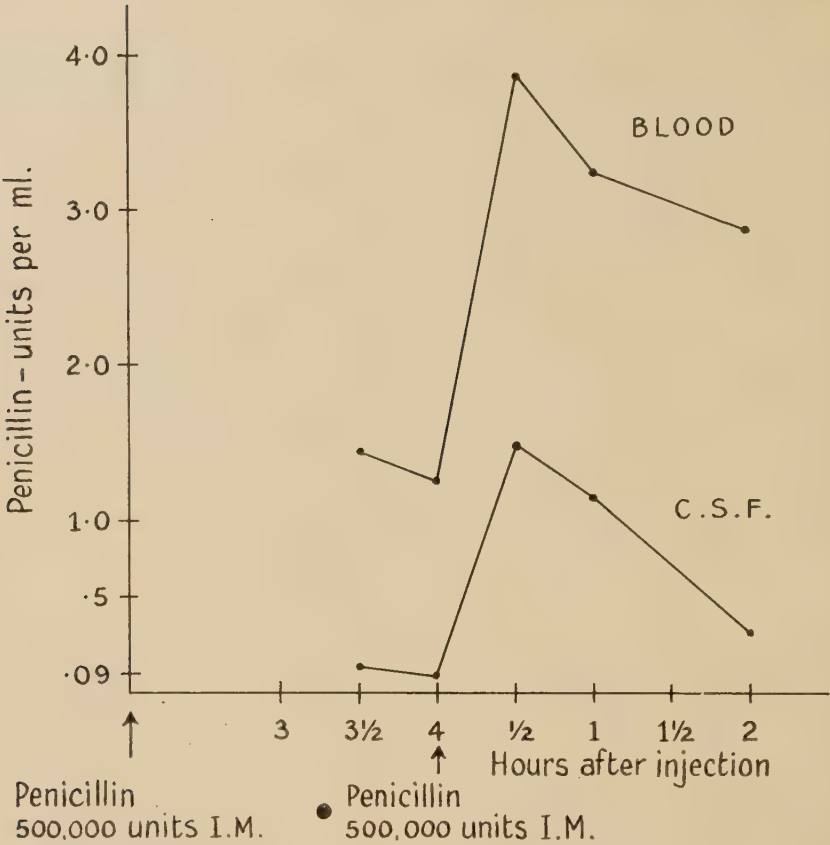
Table V indicates the qualitative results. Table VI indicates the blood serum and cerebrospinal fluid concentrations per ml.

Graphs 1, 2, 3 and 4 indicate the quantitative determinations of penicillin in the blood and cerebrospinal fluids.

It will be noted that in Cases 9 and 10 specimens of blood and cerebrospinal fluid were obtained at 3 and $3\frac{1}{2}$ hours respectively after injection. After taking specimens at the 4th hour in each case, second injections of 500,000 units were given. Thereafter specimens of blood and cerebrospinal fluid were obtained at $\frac{1}{2}$, 1, $1\frac{1}{2}$ hours in Case 10, and at $\frac{1}{2}$, 1, $1\frac{1}{2}$ and 2 hours in Case 9. It was found that when the penicillin concentration was high in the blood



GRAPH 2.—Penicillin levels in body fluids. Case 9, female, aged 52. Diagnosis: *Tuberculosis dorsalis*.

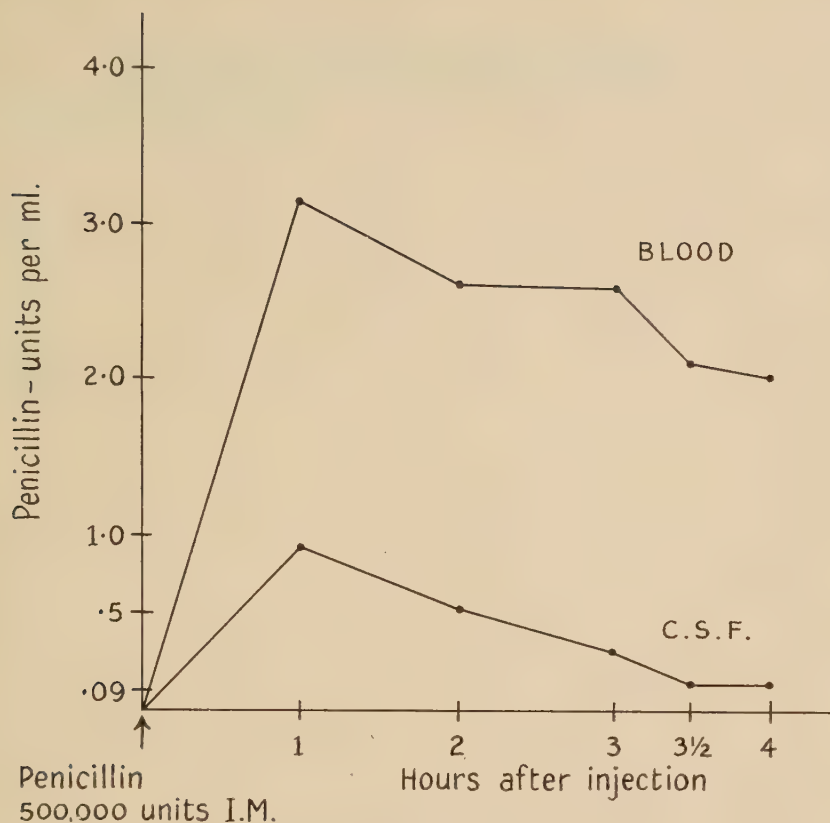


GRAPH 3.—Penicillin levels in body fluids. Case 10, female, aged 40. Diagnosis : General paralysis of the insane.

there was a significant amount of penicillin in the cerebrospinal fluid. It will be noted that in the four patients studied, penicillin was found in the blood and cerebrospinal fluids for 4 hours.

TABLE V.—Group C (high dosage). Qualitative Results of Tests for Penicillin in Blood and Cerebrospinal Fluid after Intramuscular Injection of 500,000 Units of Penicillin.

			Intervals in hours after injection.												
			Specimen.	1st injection.								2nd injection.			
				1	1½	2	2½	3	3½	4	½	1	1½	2	
Case 8	G.P.I.	Blood		+	+	+	+	+	+	+					
(female)		C.S.F.		+	+	+	+	+	+	+					
Case 9	Tabes	Blood						+	+	+	+	+	+	+	+
(female)	dorsalis	C.S.F.						+	+	+	+	+	+	+	+
Case 10	G.P.I.	Blood							+	+	+	+	+		
(female)		C.S.F.							+	+	+	+	+		
Case 11	G.P.I.	Blood		+		+		+	+	+					
(female)		C.S.F.		+		+		+	+	+					



GRAPH 4.—Penicillin levels in body fluids. Case 11, female, aged 48. Diagnosis: General paralysis of the insane.

Group D (high dosage).

One woman with tabes dorsalis (Case 12), one man with tabo-paresis (Case 13), three women with G.P.I. (Cases 14, 15 and 16), were being treated by the large dosage schedule as outlined for patients in Group C. On the morning of the 4th day of treatment a single injection each of 1 million units of penicillin was given. Specimens of blood and cerebrospinal fluid were taken at varying intervals afterwards. During the first 3 days small doses were given to prevent Herxheimer reactions.

Table VII indicates the qualitative results. Table VIII indicates the blood serum and cerebrospinal fluid concentrations per ml.

Graphs 5, 6, 7 and 8 show in graphic form the results obtained.

It will be noted that in three of the patients penicillin was detected in the blood and cerebrospinal fluids from $5\frac{1}{2}$ to 6 hours after injection.

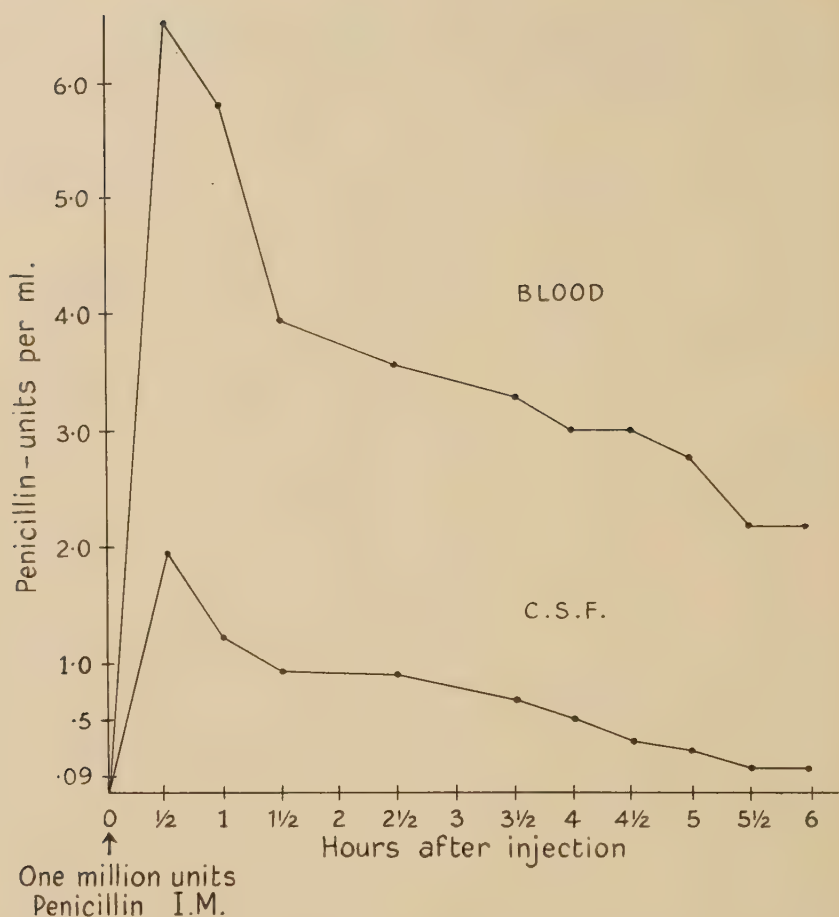
PERMEABILITY OF THE BLOOD-CEREBROSPINAL-FLUID BARRIER TO BROMIDE.

Much work has been carried out in connection with the penetration of various drugs into the brain. The bromide ion is one of the most carefully investigated drugs. Studies have been made on the distribution of this substance between

the blood and the cerebrospinal fluid, and we do know that it does not reach the same concentration in the cerebrospinal fluid as in the blood serum. In certain pathological conditions of the central nervous system the distribution of bromide between the blood and the cerebrospinal fluid is

TABLE VIII.—*Group D (high dosage). Quantitative Results of Determination of Penicillin in the Blood and Cerebrospinal Fluid.*

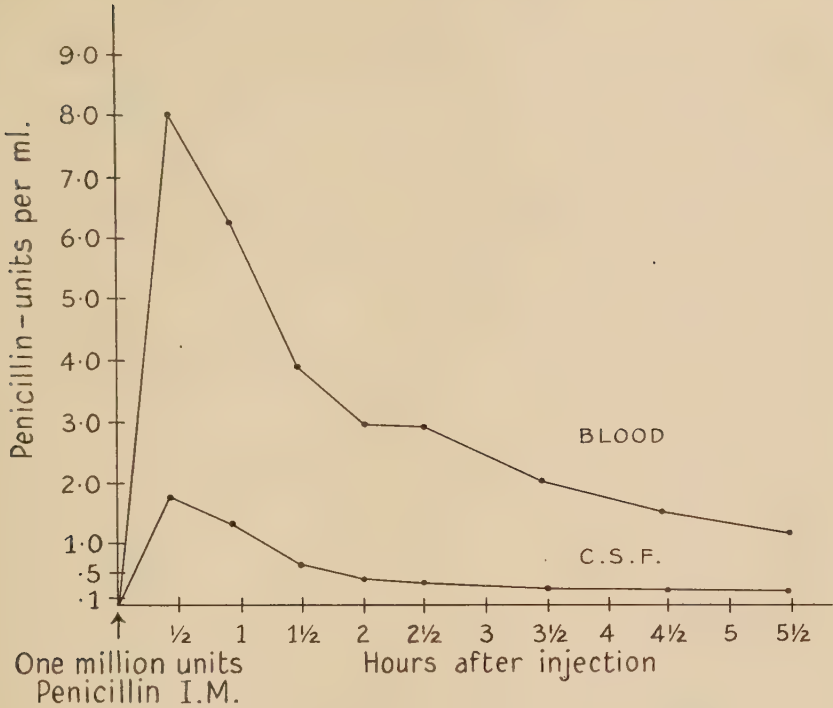
	Hours after injection.	Blood serum concentration (units per ml.).	C.S.F. concentration (units per ml.).
Case 12, tabes dorsalis (female)	$\frac{1}{2}$	6.5	1.9
	1	5.8	1.2
	$1\frac{1}{2}$	3.9	0.9
	$2\frac{1}{2}$	3.5	0.9
	$3\frac{1}{2}$	3.2	0.65
	4	2.9	0.5
	$4\frac{1}{2}$	2.9	0.3
	5	2.6	0.19
	$5\frac{1}{2}$	2.0	0.09
	6	2.0	0.09
Case 13, tabo-paresis (male)	$\frac{1}{2}$	8.0	1.8
	1	6.2	.6
	$1\frac{1}{2}$	4.0	0.7
	2	3.0	0.5
	$2\frac{1}{2}$	3.0	0.5
	$3\frac{1}{2}$	2.1	0.27
	$4\frac{1}{2}$	1.7	0.2
	$5\frac{1}{2}$	1.5	0.19
Case 14, G.P.I. (female)	$\frac{1}{2}$	8.4	1.4
	$\frac{3}{4}$	7.6	1.2
	1	6.2	1.2
	$1\frac{1}{4}$	4.7	0.9
	$1\frac{1}{2}$	4.2	0.5
	$2\frac{1}{2}$	3.8	0.2
	3	3.4	0.2
Case 15, G.P.I. (female)	$\frac{1}{2}$	7.0	1.5
	1	6.5	0.9
	2	5.5	0.9
	3	3.4	0.5
Case 16, G.P.I. (female)	5	2.0	0.12
	$5\frac{1}{2}$	1.0	0.06
	6	1.0	0.03
	$6\frac{1}{2}$	1.0	0.03



GRAPH 5.—Penicillin levels in body fluids. Case 12, female, aged 45. Diagnosis: *Tabes dorsalis*.

materially altered; the direction of the change is an increased permeability of the drug into the cerebrospinal fluid. It was thought to be of interest to study the permeability of the blood-cerebrospinal-fluid barrier to bromide in the patients of Groups C and D. This was carried out according to the method of Walter described by Ström-Olsen and Kite (1942). The patient is given .01 gr. sodium bromide per lb. body-weight, three times daily for 5 days. On the sixth day blood and cerebrospinal fluid are withdrawn. The deproteinized specimens are then treated with $\frac{1}{2}$ per cent. gold chloride solution and matched in a colorimeter. The normal ratio of bromide between blood and cerebrospinal fluid ranges from 2.8 to 3.3. This test has been used largely to determine the permeability of the blood-cerebrospinal fluid barrier. Values below 2.8 are regarded as pathological and indicate increased permeability.

Two days before penicillin treatment commenced each patient in the series (Groups C and D) was given a mixture with the appropriate bromide dose



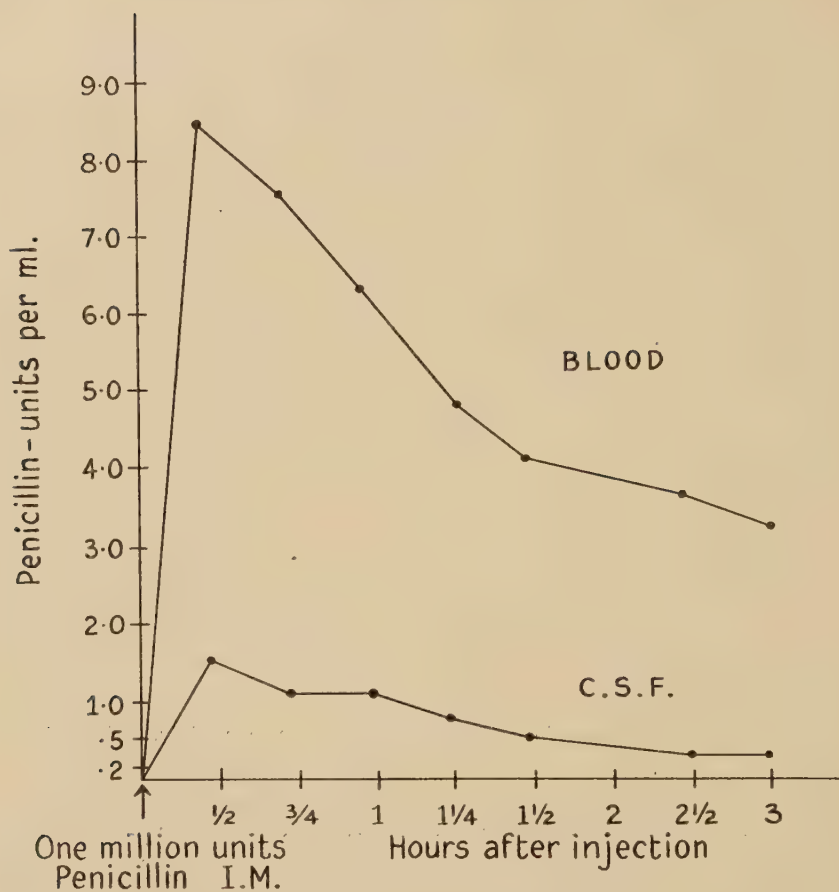
GRAPH 6.—Penicillin levels in body fluids. Case 13, male, aged 47. Diagnosis : Tabo-paresis.

thrice daily. This was continued for 5 days. On the 6th day (i.e. the 4th day of penicillin treatment), the first specimens of blood and cerebrospinal fluid for penicillin estimations were also tested for bromide. Previous laboratory studies showed that the presence of bromide in the body fluids did not inactivate penicillin.

In Table IX are enumerated the results. In the 9 patients an increased permeability to bromide was demonstrated.

TABLE IX.—Group C : Cerebrospinal Fluid Formulae and the Bromide Ratio.

	Sex.	Age.		Colloidal gold.	Protein mgm. per 100 ml.	Cells per c.mm.	Kahn.	Bromide ratio.
Group C.								
Case 8	Female	47	G.P.I.	5555543210	80	17	+++	2.0
" 9	"	52	Tabes	2223322110	40	56	+++	2.5
" 10	"	40	G.P.I.	5554332100	45	58	++++	2.4
" 11	"	48	G.P.I.	5554322110	48	13	++	2.8
Group D.								
Case 12	Female	45	Tabes	2233321100	50	35	+++	2.5
" 13	Male	47	Tabo-paresis	5555432210	36	22	+++	2.1
" 14	Female	47	G.P.I.	5555432000	90	20	+++	2.6
" 15	"	63	"	5554321000	46	16	+++	2.0
" 16	"	53	"	5555432110	40	10	++	2.48



GRAPH 7.—Penicillin levels in body fluids. Case 14, female, aged 47. Diagnosis : General paralysis of the insane.

SUMMARY OF RESULTS.

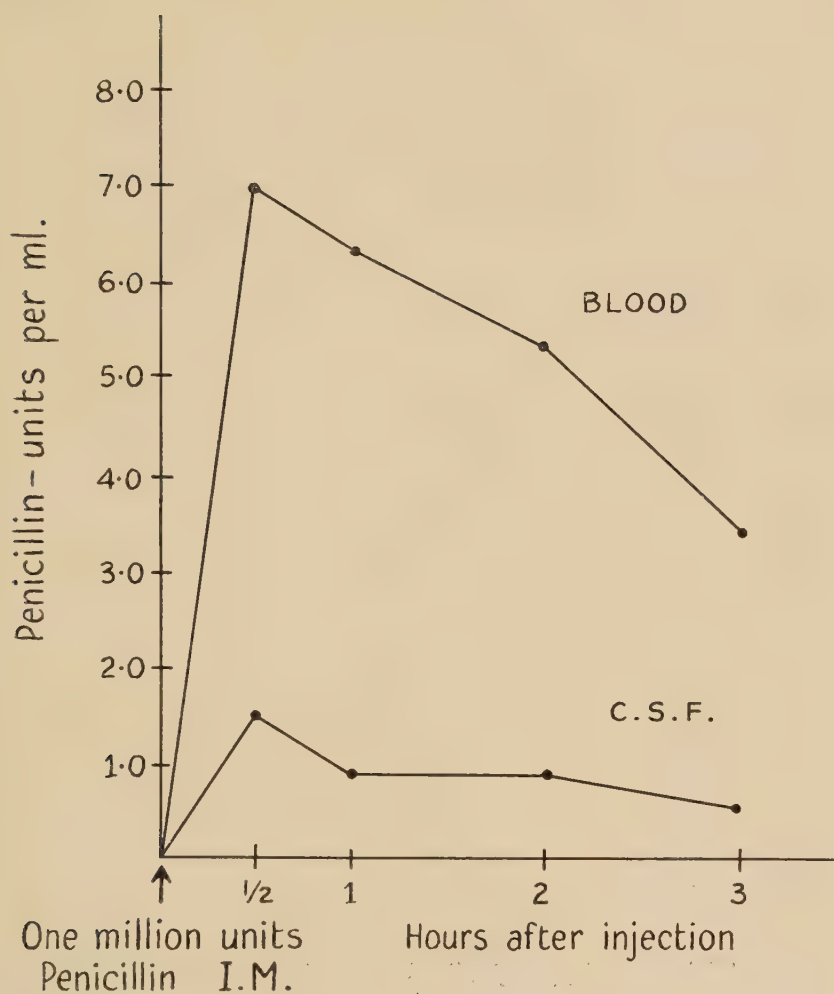
As shown in Tables I, II, III and IV, penicillin could not be detected in the cerebrospinal fluids of the 7 patients belonging to the lower dosage groups, A and B. Altogether 42 specimens of cerebrospinal fluid were examined.

Thirty specimens of blood were examined. One patient had a maximum concentration of 0.860 unit per ml. half an hour after 50,000 units of penicillin intramuscularly. The other four patients had maximum blood concentrations below this level.

Tables V, VI, VII and VIII show that in the higher dosage groups C and D, penicillin was found in the 33 specimens of cerebrospinal fluid and the 33 specimens of blood examined.

In Group C one patient had a maximum serum concentration of 4 units per ml. one hour after injection of 500,000 units of penicillin. The other 3 patients at one hour showed maximum concentrations below this level.

One patient had a maximum cerebrospinal fluid concentration of 1.1 unit. The other 3 had maximum concentrations below this at one hour.



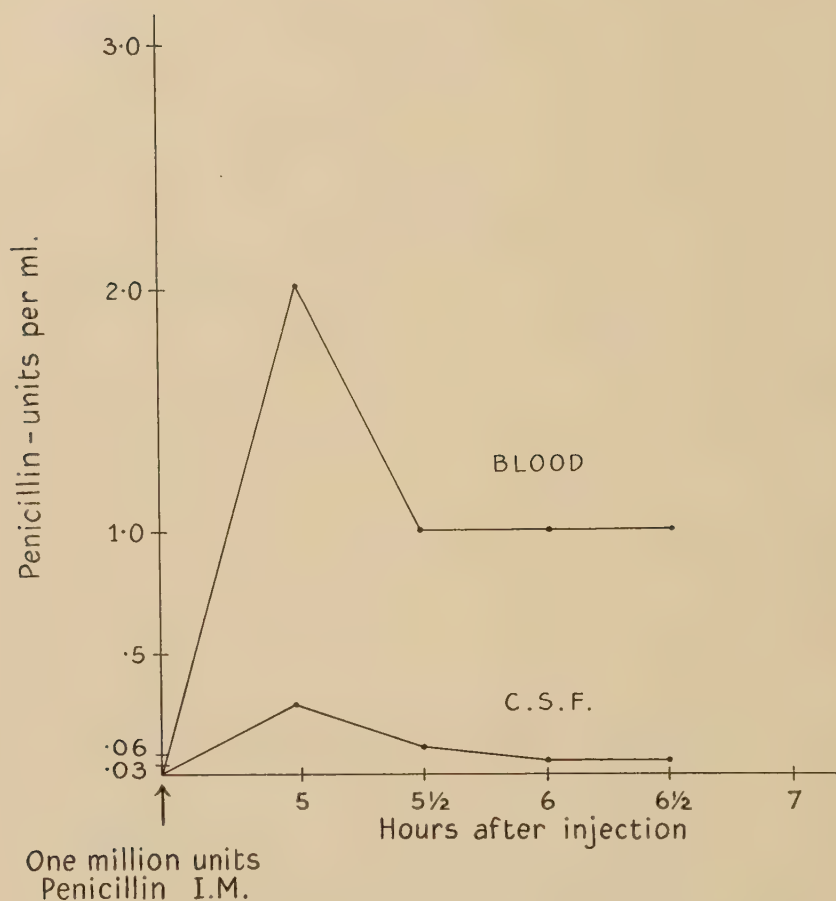
GRAPH 8.—Penicillin levels in body fluids. Case 15, female, aged 63. Diagnosis : General paralysis of the insane.

The minimum serum concentrations of 1.2 units per ml. were found in Cases 8 and 10 at the 4th hour after injection. The cerebrospinal fluid concentration at this time was 0.09 units per ml. in Case 8 and 0.05 units per ml. in Case 10. The latter was the lowest amount detected in the cerebrospinal fluids of the 4 cases.

One hour after injection of 500,000 units the average blood serum concentrations for the 4 patients was 3.5 units per ml., the average cerebrospinal fluid concentration at this time 0.4 units per ml.

Four hours after, the average blood serum concentration for the 4 patients was 1.5 units per ml. while the average cerebrospinal fluid concentration was 0.08 units per ml.

In Group D, one patient had a maximum serum concentration of 8.4 units per ml. half an hour after injection of one million units of penicillin. Three



GRAPH 9.—Penicillin levels in body fluids. Case 16, female, aged 53. Diagnosis : General paralysis of the insane.

other patients showed maximum concentrations below this. One patient had a maximum cerebrospinal fluid concentration of 1.9 units per ml. half an hour after injection.

The minimum serum concentration of 1.0 unit was found in Case 16, at 6½ hours after injection of one million units. The cerebrospinal fluid concentration at this time was 0.03 units. This was the lowest amount detected in the cerebrospinal fluids of the 5 cases.

Half an hour after injection of one million units of penicillin the average blood serum concentration for 4 patients in this group was 7.5 units per ml. The average cerebrospinal fluid concentration in these 4 patients at this time was 1.6 units per ml. The average blood serum concentrations for 3 patients in this group 5½ hours after one million units was 1.5 units per ml. The average cerebrospinal fluid concentrations at this time in these 3 patients was .08 units per ml.

DISCUSSION.

If a drug is detected in the cerebrospinal fluid this is no reliable indication that it has penetrated the blood-brain barrier. Failure to detect a compound in the cerebrospinal fluid does not mean that it has not passed into the nervous system via the blood-brain barrier. It may have been in effective concentration in the perivascular and pericellular spaces of the brain; but on reaching the subarachnoid space it may have become diluted in the bulk of the cerebrospinal fluid so as to be no longer detectable. We can say that if penicillin is not detected in the cerebrospinal fluid, then not all nervous tissue is being reached.

Wallace and Brodie (1940) in experiments on dogs, showed that following injections of bromide and iodide the extra-cellular fluid derived from the perivascular spaces of the brain 8 minutes after injection, contains concentrations of the ion equal to that of the ventricular fluid and concentrations greater than that of the fluid in the cisterna magna. Also, when the passage of the cerebrospinal fluid from the cisterna magna to the spinal subarachnoid space was blocked by ligature, the fluid below the ligature takes up appreciable amounts of the ion which was injected intravenously; thus showing that the drug must have come directly from the spinal cord vessels. They came to the conclusion that bromide and iodide enter the cerebrospinal fluid as readily from the capillaries in the brain substance as from the choroid plexus vessels and that part of the effect due to the cerebrospinal fluid barrier is connected with the intra-cerebral and intra-spinal capillaries, i.e. the blood-brain barrier.

In the 9 cases of Groups C and D, bromide was detected in the cerebrospinal fluid in increased amounts because of the increased permeability. Penicillin was also found in appreciable amounts. If we accept the findings of Wallace and Brodie, that part of the effect due to the cerebrospinal fluid barrier is connected with the blood-brain barrier, then it is reasonable to infer that penicillin which had penetrated into the cerebrospinal fluid had also penetrated the blood-brain barrier.

Clinically and serologically the patients treated with the large doses of penicillin showed remarkable improvement.

The study confirmed the observations of others, that penicillin given in small intramuscular doses to cases of parenchymatous neurosyphilis cannot be detected in the cerebrospinal fluid; when it is given in large doses it enters the cerebrospinal fluid.

When the blood penicillin reaches a high concentration the cerebrospinal fluid soon reflects the increase. All the cases in Groups C and D demonstrated this. Of particular interest were Cases 9 and 10 (see Graphs 2 and 3), where 4 hours after 500,000 units, the blood and cerebrospinal fluid levels were low, a second injection of the same dosage quickly brought the levels higher.

From the findings a scheme of dosage for the treatment of parenchymatous neurosyphilis can be suggested. In 4 of the patients an intramuscular dose of 500,000 units gave rise to appreciable amounts of penicillin in the cerebrospinal fluid continuously for 4 hours. At the end of this period when the serum

concentration was becoming low the cerebrospinal fluid level was dropping. It seems justifiable to space the doses at this interval when these doses are used.

In 2 of the patients an intramuscular dose of 1,000,000 units gave rise to appreciable amounts in the cerebrospinal fluid continuously for 6 hours when the level then became low. This interval is suggested if these doses are used.

The penicillin level in the cerebrospinal fluid seems to depend on the level of the drug in the blood serum. When this is high adequate amounts appear in the cerebrospinal fluid. If it is low only small amounts or none at all appear in the cerebrospinal fluid.

In the light of experience based on this research the writer now treats patients suffering from parenchymatous neurosyphilis with the following dosage :

1st day	20,000	3-hourly	for 8 doses.
2nd „	50,000	3	„ 8 „
3rd „	100,000	3	„ 8 „
4th-10th „	500,000	4	„ 42 „

During the past two years 20 patients (this includes 9 patients in the present series) have been treated with this dosage. Herxheimer reactions have not occurred and there have been no signs of any meningeal irritation or convulsions.

SUMMARY.

Sixteen patients with parenchymatous neurosyphilis have been treated by penicillin administered intramuscularly.

Observations on the penicillin content of the blood and cerebrospinal fluid after small and large doses have been made. When small doses are given detectable amounts of penicillin appear in the blood serum, but no penicillin enters the cerebrospinal fluid.

When large doses are given large amounts of penicillin can be detected in the blood serum and penicillin then enters the cerebrospinal fluid.

From the results of the investigation a scheme of dosage is suggested for the treatment of parenchymatous neurosyphilis.

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FIFTY CASES OF EPILEPSY TREATED WITH "TRIDIONE."

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INTRODUCTION.

Tridione is established as by far the most powerful drug in the control of *petit mal*. Many of its clinical aspects, therapeutic as well as toxic, are as yet not clear. In spite of this there is a remarkable absence of reports on the use of it in controlled clinical experiments.

Most of the reports on clinical trials with tridione have come from the U.S.A. After its anticonvulsant properties were established in animal experiments by Everett and Richards (1944), Lennox (1945) and Perlstein (1945) were the first to administer it in cases of human epilepsy. Lennox (1947) analysed a series of 300 patients who had the treatment over a period of up to two years. De Jong (1946) tried the drug in cases with psycho-motor attacks. Perlstein (1945) tried its effects on cases with gross organic lesions in the central nervous system, such as cerebral palsies of various etiology, tetanus, chorea, etc. He also gave the drug to patients showing behaviour disorders. He did not give a detailed description of the latter, but came to the conclusion that tridione controls the symptoms of lesions in the extra-pyramidal system, in which group he included behaviour disorders. Thorn (1945) also used tridione on a small number of cases with organic lesions of the central nervous system. His series included cases with familial mental deficiency, birth trauma, microcephaly, post-encephalitic cases and deteriorated epileptics. However, he merely observed the effect of the treatment on the major seizures accompanying these conditions. In this country clinical reports are very few, and with one or two exceptions they stress the adverse effects of the drug rather than analyse its therapeutics.* It came about, therefore, that the general trend was always to over-emphasize the dangers of the treatment. It led even to the repudiation of tridione: as it was put in one paper, "In this short series (10 patients) the toxic complications of tridione proved more dangerous than the disease it is used to treat." It is for this reason that it was decided to publish the experience with tridione in a series of 50 patients, treated both as in- and out-patients at the Maudsley Hospital, London. Most of these were patients in the epileptic clinic at that hospital.

* Since this report was written two papers have appeared in the *Brit. Med. J.* and one in *Brain*: Whitty, C. W. H., *Brit. Med. J.*, 1949, 6 August, Haward, F. C., *ibid.* Davies, G. R., and Spillane, J. D., *Brain*, 1949, 72 II, 140.

CASE MATERIAL.

The group consisted of 31 adults, their ages ranging from 16 to 52 years, and 19 children aged from 4 to 16 years. Twenty-six were male and 24 female patients.

Clinically this group was heterogeneous. Eight cases had either *petit mal* only, accompanied by a 3 cycle-per-second wave and spike (c/sec. W.S.) pattern in the electroencephalogram (E.E.G.), or else *petit mal*, myoclonic jerks and akinetic attacks, also accompanied by the 3 c/sec. W.S. pattern in the E.E.G. One case had wave-and-spike variant (2 c/sec.). There were a further 5 in whom attacks were clinically indistinguishable from *petit mal*, but the E.E.G. did not show any specific epileptic wave forms. In every patient there were from 5 to 8 E.E.G. recordings done at varying intervals from 1 to 3 months. The largest group consisted of 29 cases who had had in the course of their illness more than one type of attack. All of these suffered from major attacks, although in some cases these were only reported to have occurred once or twice in their lives. Twenty-one of them suffered from *petit mal* attacks, the E.E.Gs. in 7 cases showing the 3 c/sec. W.S. pattern. Four showed the wave-and-spike variant (2 c/sec.). Of those in whom psychomotor attacks were prominent, namely 9 cases, 3 showed W.S. in the E.E.G. recordings, 2 had W.S. variants, and 4 had no specific wave forms. Ten cases of this "mixed" group suffered from myoclonic jerks, 5 with W.S. forms, 5 without. One case had true akinetic attacks. In this case the W.S. was never found in the E.E.G. A further 7 cases showed signs of organic lesions in the central nervous system. These will be described in detail separately.

DOSAGE.

The recommendations for dosage vary widely in the various reports. Probably, as a result of the preoccupation with the adverse effects, the papers which appeared in this country recommend rather low doses. Butter (1948) suggests that the daily dose should not exceed 4 capsules (1.2 g.). In the present series the following doses were given without serious adverse effects:

8 capsules (2.4 g.)	per day to 1 patient for 4 months.
6 " (1.8 g.)	" 2 patients for 6 months.
5 " (1.5 g.)	" 9 patients for periods from 1 month to 1 year.
4 " (1.2 g.)	" 13 patients for periods from 2 months to 18 months.
3 " (0.9 g.)	" 25 patients for periods up to 2 years.

In none of the patients was it necessary to reduce the dosage permanently because of toxic or allergic side effects. In 2 cases difficulties arose after the first 2 to 3 weeks of treatment. In one woman glandular enlargement with malaise and slight fever occurred. She had also noticed an erythematous rash, but this had faded before she was seen by a doctor. Tridione was withheld for 2 weeks. The symptoms subsided, and on recommencement of treatment

no further difficulties occurred. To minimize the number of allergic reactions of this type, treatment was started with 2 capsules per day in adults and 1 capsule in children. This dose was increased weekly by one further capsule until optimum effects had been obtained. This gradual assessment of the most effective dose is the only way to stabilize the treatment. Whereas in many cases 3 capsules and in the majority of cases 4 capsules per day proved sufficient to abolish all attacks of *petit mal* or myoclonus, in 9 cases 5 capsules only produced a satisfactory result. How unpredictable the optimal dosage is becomes apparent if one considers that adults sometimes required small doses only, e.g. 3 capsules per day, whereas some children needed much larger doses, e.g. 5 capsules per day, to reduce the number of their attacks.

RESULTS: GENERAL.

Davies and Lennox (1946) in their tables indicate that *petit mal* attacks responded best to the treatment. In a very few of their cases (4 per cent.) an increase in the number of attacks occurred. On the other hand, of the patients with major seizures very few responded favourably (30 per cent.), some remained unchanged (30 per cent.), and many of them showed an increase in the number of fits (40 per cent.). The response of patients with psychomotor attacks was somewhere in between—improved 70 per cent., no change or worse 30 per cent. The results in this series are similar to those of Davies and Lennox as shown in Table I, except in the cases with major seizures, there the results seem to have been more favourable.

1. Major Seizures.

Table I may be misleading in regard to the major attacks. These cases were not treated by tridione alone. The patients were usually taking one or several anticonvulsants, such as phenobarbitone or epanutin in doses which had been found optimal, but did not control all attacks. When treatment with tridione was commenced, the other drugs were continued at the same time. In most cases in this series tridione did not further reduce the number of major seizures.

TABLE I.

Result of treatment.	Unmixed <i>petit mal</i> .		Mixed epilepsy.			
	With 3 c/sec. W.S.	Without 3 c/sec. W.S.	<i>Grand mal</i> seizures.	<i>Petit mal</i> with W.S.	<i>Petit mal</i> without W.S.	Psycho- motor attacks.
Worse	..	..	3 (temporarily)	..	..	..
No change	..	..	8	..	..	3
Little improvement	..	..	1	..	..	..
Number of attacks reduced by half	..	..	1	1	2	1
Number of attacks reduced by more than half	..	..	4	..	1	2
Great improvement	2	..	7	3	6	1
No further attacks	6	6	3	3	5	2

This table shows the response to treatment of the various types of attacks encountered. In the "mixed" group the types of attacks are charted, not the patients. It does not include the patients with "organic" lesions in the nervous system.

In 3 cases out of 27 the major attacks disappeared completely. In 12 they were reduced more or less. In 9 no marked change could be observed, and in 3 the number of attacks increased. In 2 of the latter no other anti-convulsant had been taken with tridione, and the major attacks ceased when phenobarbitone or epanutin was added. In the third case the previous dose of epanutin was slightly increased, and the number of attacks was reduced to its former level.

The results in these three patients are of interest. Even if tridione does seem to reduce major seizures in a small number of patients, it was obvious from the first clinical trials that it was certainly not the drug of choice in this disorder. The observation, however, that it did increase the number of attacks in some patients has often been quoted as another of the adverse effects of the drug. The fact that in these cases the attacks so precipitated were only very few should not deter from the seriousness of this argument for the following reason: some of the patients concerned were young adults and had not had major attacks since their childhood; the sudden unexpected attacks shortly after commencement of a new treatment came rather as a shock, and may well deter the disappointed patient from going on with the treatment. This can be largely prevented by giving any patient who has a history even of rare generalized convulsions a combination of tridione and phenobarbitone gr. $\frac{1}{2}$ *t.d.s.* or epanutin gr. $1\frac{1}{2}$ *b.d.* for a few weeks rather than tridione alone. These drugs can, however, after a few weeks be withdrawn gradually. Major attacks were never precipitated in patients in whom the history had not revealed any such previous attacks.

2. Psychomotor Seizures.

The effect on psychomotor attacks was particularly studied by De Jong (1946). He claimed that a combination of tridione and epanutin had a very good effect on this type of attack. In the present series of 9, 4 cases showed some reduction in the number of attacks and in 2 they have quite disappeared, but in 3 cases no apparent change was noted. All these patients took epanutin with or without phenobarbitone together with the tridione. These results are rather similar to those of De Jong, and also of Davies and Lennox (1946).

3. Minor Seizures.

In the cases of *petit mal* some improvement always occurred. In most patients attacks before treatment with tridione had been as frequent as 10-15 per day or more. In several cases they were as frequent as 3 per minute. In one case only was the reduction in the number of attacks merely slight. There was reason to suspect a lesion in the central nervous system. The patient will be mentioned again with the "organic cases." In all the other patients improvement was spectacular. In 20 cases attacks ceased altogether. The case in which there was only slight improvement is a young girl who is mildly demented, and shows a number of signs due to organic changes in the central nervous system. She is aged 19, and has a number of epileptics in her family.

She has always been backward. She began to have both major and minor fits 2 years before menarche. Some of the attacks seem to be of a hysterical nature. She has a right facial weakness and an epilepsia partialis continua of the right arm and leg. The two affected limbs show an increase in tone and tendon reflexes. The plantar reflex is doubtfully dorsiflexor on the right side. There is also some sensory loss of cortical type in the right hand. A full investigation, including an air encephalogram and arteriogram, did not reveal the character of the lesion in the central nervous system. The E.E.G. showed high voltage slow waves, especially on the left side.

4. Cases with Organic Lesions in the Central Nervous System.

Tridione was also given to a small number of patients with organic changes in the central nervous system. This aspect of the clinical application of tridione was particularly studied by Perlstein (Richards and Perlstein, 1945). The number of this type of patient in the present series is small, namely 7. They are reported here because the subject has been discussed by others, and the total number of cases reported so far is very small indeed, namely 15 cases.

(1) One patient had congenital diplegia. He is 10 years old. He is somewhat spastic in all limbs, with increased tendon reflexes and bilateral extensor plantar responses. His intellectual ability is at the level of imbecility. He had been unruly at home, dirty, aggressive towards his sister, and had never been to school. He suffered from frequent myoclonic jerks and extremely numerous *petit mal* attacks. From time to time, about once per week, he would have what is best described as *petit mal* status epilepticus. During this there was no appreciable interval between attacks. His E.E.G. was a continuous 2-2½ c/sec. W.S. variant. Phenobarbitone and epanutin were tried, but produced no great change. After treatment with tridione his myoclonic jerks and most *petit mal* attacks ceased. He still goes into the status epilepticus described above, but only once a month or less frequently. He is much more manageable at home, goes now to a play centre, plays with other children and seems much brighter. His neurological signs, however, have not changed.

(2) Another child with cerebral diplegia and W.S. forms on the E.E.G. had no further attacks of *petit mal* when under treatment, but his major seizures increased somewhat in number. They were easily controlled by epanutin. His neurological signs have not changed as the result of treatment.

(3) The next three cases showed evidence of organic dementia, but no persisting localizing signs were present on neurological examination. One of them had epilepsia partialis continua. The pneumo-encephalogram and other methods of investigation did not reveal any cause. She has shown slowly progressing dementia since the age of 14. Tridione reduced the number of her *petit mal* attacks slightly, but did not improve her general condition very much. The other two cases were affected in a similar way: their *petit mal* attacks were greatly reduced, almost abolished; the other aspects of their illness, i.e., the dementia and the other types of fits, were little affected.

(4) One patient was suffering from Unverricht's type of myoclonus epilepsy in an advanced state. Her condition did not change the pace of its progress, but all her attacks, *petit mal*, myoclonus and *grand mal* stopped completely while she was under treatment. They did recur when the tridione was withheld for a few weeks, although treatment by epanutin and phenobarbitone had been continued. Among other marked symptoms this patient had dysphagia. At the height of this she could not swallow at all. With tridione this symptom subsided almost completely, only to recur if the dose was reduced. This patient took 6 capsules daily.

(5) There was one case who suffered from epilepsy due to a cerebral tumour. Attacks were markedly reduced by tridione. Later the tumour was removed by operation, but the fits continued. The fits were mainly of the *petit mal* type. Treatment was again started after operation, and was again helpful.

THE E.E.G. AND EFFICIENCY OF TRIDIONE.

Lennox (1947) points out that the best results of the treatment can be obtained in cases belonging to the so-called "Triad." By this is meant any of the attacks which are commonly accompanied by the 3 c/sec. W.S. pattern in the E.E.G., namely *petit mal*, myoclonic jerks and akinetic attacks. Lennox goes so far as to describe tridione a specific treatment for this condition. The present series has been analysed from this point of view (Table II).

TABLE II.

Results of treatment.	Unmixed <i>petit mal</i> .		Mixed epilepsy.	
	With 3 c/sec. W.S.	Without 3 c/sec. W.S.	With 3 c/sec. W.S.	Without 3 c/sec. W.S.
No further attacks . . .	6	6	3	5
Less than one attack per month . . .	2	—	3	6
Less than one attack per day . . .	—	—	1	2
Several attacks per day . .	—	—	—	1

The figures indicate the number of patients in the various groups who have minor seizures.

The patients who have W.S. patterns in their E.E.G. show a slightly better response than those without it. Nearly two-thirds of the cases with W.S. showed a complete disappearance as against half without W.S. forms. Reduction to a level rarer than one attack per month is about equal in the two groups, and the cases who did not improve beyond one attack per day were all without the W.S. The therapeutic efficacy is also slightly less in patients who suffer other types of seizure in addition to *petit mal*. In most of these cases other drugs had been tried, but had little or no effect in reducing the *petit mal* attacks. In a few cases only was tridione used as the first drug to be tried.

It would appear then that tridione can be expected to produce results in patients suffering from *petit mal*, either alone or with other forms of epilepsy. Cases in which the E.E.G. shows W.S. forms have a slightly better prognosis. The danger of precipitating major seizures in mixed cases or in patients who have had a few major convulsions at any time in the past does exist. This can, however, be prevented by adding phenobarbitone or epanutin, and can easily be treated should it occur unexpectedly.

Table III shows that patients in whom the W.S. pattern is present in the E.E.G. do not require smaller doses of tridione to achieve optimal therapeutic success.

TABLE III.

Type of epilepsy.	Cases showing the 3 c/sec. W.S. in E.E.G.	Cases not showing the 3 c/sec. W.S. in E.E.G.
Unmixed <i>petit mal</i> . . .	3-4 caps. per day	4 caps. per day
Mixed epilepsy . . .	5 caps.	4-5 caps.
Symptomatic epilepsy ("Organic" cases) . . .	5-6 caps.	4 caps.

The figures indicate the average number of capsules per day necessary to suppress the largest number of *petit mal* attacks. Each capsule contains 0.3 g. of tridione. The effects of these doses were not necessarily equivalent.

TRIDIONE AND "BACKWARDNESS" IN EPILEPTIC CHILDREN.

Another very striking effect of the treatment was the apparent change in the intellectual abilities of some patients, particularly of children. In a number of children suffering from *petit mal*, the school authorities reported that the children were backward in their class, that they had had to be transferred to a lower stream* in the school, and were still unable to benefit from the instruction. The school authorities were considering their transfer to special schools for backward children.

In four of these children the treatment produced excellent results. The frequent minor seizures ceased and the children caught up quickly with their work. Soon they could be moved up to a higher stream and were able to continue at their schools.

In spite of this striking change in performance in learning, psychometric tests did not show any alteration in their intelligence quotient (I.Q.). This apparent discrepancy may be explained by the fact that in patients suffering from *petit mal* consciousness is more disturbed than is clinically evident. The so-called "subclinical attacks" observed in the E.E.G. probably manifest themselves in this way: that the child cannot cope as well as other children in a competitive situation such as everyday school life presents, but the individual attention of the psychologist during the test helps the child to perform according to his mental age level. It was interesting to note that in these cases the E.E.G. records showed marked improvement as treatment went on. There were fewer bursts of epileptic activity.

ADVERSE EFFECTS OF TRIDIONE.

There are several adverse effects of this drug. They have been described by most of the previous writers on tridione. Most of them are harmless if detected early, and in the case of most, treatment need not even be interrupted.

(1) *Glare or hemeralopia*.—This symptom occurs in a rather large number of patients who take tridione. Lennox (1947) reports that in his series adults only suffered from "glare." In our series 11 patients (20 per cent.) had it. Half of these were patients below the age of 15 years. The symptom is troublesome, as it exposes the patient to the risk of accidents when entering the bright street from a dark house, tube station, etc. The symptom disappears sometimes spontaneously after a few months. If not, a pair of dark glasses will usually help. Most authors report that no retinal changes can be observed. In the present series the patients had repeated ophthalmoscopic examinations, but no abnormalities were found. The cause for the glare, however, is probably not in the retina or optic nerve at all, but more central. The symptom is similar to that which sometimes occurs as a toxic effect of digitalis. Carroll (1945) has described glare in a number of patients, some of whom showed hemianopic distribution of the symptom, or the glare alternating with a hemianopia. Both subsided when treatment was stopped.

* In some schools each age group (class) is subdivided into "streams" A, B, C or D. Those divisions are made on the basis of intelligence tests.

(2) *Skin conditions*.—In several patients transient maculo-papular rashes appeared particularly on the forehead, behind the ears, on the chest and over the arms. These disappeared even if tridione was only reduced to 2 to 3 capsules per day. The first patient in this country whose death was alleged to have been caused by tridione was a little girl who died of exfoliative dermatitis, reported by Keren (1948). She had a rash which was at first mistaken for scarlatina. When it appeared the dose of tridione was increased and continued for nine days. Blood counts which were done from the peripheral blood near death were normal (personal communication). This is the only case of that kind reported anywhere. In our series mild erythematous rashes occurred in seven cases only. Two further cases had angioneurotic oedema shortly after commencement of the treatment. It is difficult to decide whether tridione was really the cause of the latter.

(3) *Kidney affections*.—These have been reported by two authors (Briggs *et al.*, 1949; Barnett *et al.*, 1948). No such effect was observed in this series. One of the cases reported in the literature was fatal, the other recovered after tridione had been discontinued.

(4) *Behaviour difficulties* are reported in the literature to have been brought on by treatment with tridione in children as well as in adults. In other patients, however, behaviour abnormalities are reported to have been alleviated. In our series two boys were apparently difficult in school. They ill-treated animals, beat other children, etc., and were not improved by ordinary methods. Tridione not only stopped their attacks, but brought improvement in their behaviour. In one case, a boy of 10, the mother reported that after the treatment began he became very restless and noisy and was more difficult to manage. The treatment was continued nevertheless, and after a few weeks the boy's behaviour became normal again; his frequent seizures had ceased.

(5) *Blood*.—The blood changes have received more attention than the other side effects of the drug, because the first fatalities following the administration of the drug were due to them. In the present series only one patient had a severe but transient leucopenia of 1600 W.B.C. Tridione was withheld for two weeks and then given again without any ill effects. The white cell-count returned to normal. The patient suffered no symptoms during this period.

Blood counts, including differential counts, were carried out once per month in every patient. In addition every patient was asked to report to the hospital if any of the symptoms which might suggest agranulocytosis, such as sore throat, malaise, petechiae, etc., should occur. This did not happen.

Further investigations of the blood are discussed more fully later.

COURSE OF TREATMENT.

It has been repeatedly pointed out that tridione is different from most drugs used in epilepsy in that it does not precipitate large numbers of attacks or even status epilepticus if it is suddenly withdrawn. No attacks are precipitated by the withdrawal. On the contrary the therapeutic effect may be maintained for several months. This is important, because the drug can be withheld suddenly if adverse effects are noted, and also because the patient

is not exposed to any danger if he unexpectedly runs out of capsules and cannot readily replace them.

Lennox (1947) observed that the benefit gained by the treatment was not only held temporarily if the treatment was interrupted, but was often maintained permanently. Quite early on in our series a mother reported that she had deliberately withheld treatment because the patient, a 10-year-old boy, had not had a single attack for many months. He had suffered up to 20 or 30 attacks a day. In spite of the fact that the patient had not taken any tridione for the past month his attacks had not reappeared. He had been taking 4 capsules per day for six months. It was decided that treatment should be withheld until attacks would return. The patient was asked to report monthly to the clinic. He has done so for the past 13 months. This does not, however, occur in many cases. The drug was withheld in a number of patients, but only in a few did the attacks remain abolished. In none, however, did the condition relapse to a pre-treatment level. Some improvement was maintained in all cases. It is also probable that the length of treatment is of significance. Six months appears the minimum for which treatment has to be maintained before one can expect the benefit to remain permanent.

The best way to administer the drug seems to be as follows: The number of capsules per day is gradually increased until the maximum therapeutic effect is obtained. It may be necessary to give as many as 8 capsules per day. Children over 5 years seem to tolerate these doses quite well, although one would observe greater caution. This dose should be maintained for 1 to 2 months if the seizures are abolished. The drug should then be reduced to a lower level by 1 capsule per day every month. Should attacks recur the dose is increased again. After six months the dose can be reduced to 3 capsules per day. One daily capsule should be withdrawn every two months from then on. Should attacks recur at any of these stages no further reductions should be made, or the dose should be increased again if necessary.

BLOOD CHANGES.

An analysis from the literature of the cases in which tridione seems to have caused death due to blood changes shows the following encouraging fact: Although tridione must have been administered to tens of thousands of patients, as Lennox states, and has been in clinical use for several years, only five patients are described in the literature in whom the drug was alleged to have caused death by affecting the blood-forming organs or the blood.

One case described by Harrison, Johnson and Ayer (1946) was not taking tridione alone, but also mesantoin. At the time of publication of this case no fatalities had been described following mesantoin, and so the blame for the unfortunate issue in this patient was squarely put on the shoulders of tridione, but since then a case of aplastic anaemia occurring in a patient taking mesantoin alone was published by Bloom, Lynch and Brick (1948).

The second case was described by Mackay and Gottstein (1946), the third and fourth case in this country by Forster, Watson and Neumark (1949), and by Braithwaite (1948); the fifth case was briefly mentioned in *The Lancet*

(1947). In all the fully reported cases the peripheral blood was very markedly affected. It showed a gross diminution of granulocytic cells. The red blood cells were also reduced. In one case the bone marrow did not show any gross abnormality, and showed even a hyperplasia of the erythroblastic elements. In the other the bone marrow showed hypoplasia, and in the third the report was inconclusive. In the latter immature granulocytes were found in the peripheral blood. A third case described by Greaves (1946), although not fatal, may well be added here. This patient, who took tridione combined only with phenobarbitone, developed a granulocytopenia. He recovered on discontinuing tridione, but relapsed promptly on attempting to start it again. It was eventually abandoned. Nothing was said about the state of the bone marrow in this case.

Davies and Lennox (1946) found that even when the cell count of the neutrophil polymorphonuclear cells fall to very low levels, grave effects do not always accompany this. They report that in some of their patients the neutrophils fell as low as 1600. Tridione was continued in a number of these, but no ill-effects followed. The patients had no complaints. It appears then that tridione has a selective depressant effect on certain elements in the blood, mainly on the neutrophil polymorphonuclear cells, but that occurs only in a small number of patients, and it is then mostly only transitory and asymptomatic. Only a very small number show symptoms of a grave illness, and in even fewer does it remain irreversible.

Young (1949) states that by the time the peripheral blood shows leucopenia in cases of agranulocytosis the bone marrow changes are well established. If that is so the leucopenia described in our cases is only transitory, and has nothing in common with the severe irreversible type. It is harmless, and does not require any treatment. Indeed recovery occurs even if the drug is not withheld. Young says this type of leucopenia is not due to the toxicity of the drug itself. The fact that the bone marrow in the case of Mackay *et al.* was not very abnormal is not conclusive either. It does not necessarily mean that the case is one of peripheral destruction of the neutrophil polymorphonuclear cells. It may be a true central agranulocytosis in which the bone marrow has begun to recover again.

EOSINOPHILIA.

In only one of our cases did a severe leucopenia occur. The W.B.C. fell to 1600, but there were no symptoms. However, in the present series other changes in the blood have been observed, which may have some important connection with the above group of cases. Sixty per cent. of our cases treated with tridione showed an increase in their eosinophil counts shortly after commencement of the treatment (Table IV).

In about half of those who showed eosinophilia it subsided again after a few weeks or months in spite of continuation of the treatment. In one case it disappeared after cessation of tridione therapy, and did not reappear on resumption of it.

Robinson (1947) in his report on 100 cases mentions occurrence of eosinophilia, and attributes it to other causes unconnected with the drug. In Hall's

TABLE IV.

Number of case.	Eosinophils before treatment.	Eosinophils during treatment.	Time in which eosinophilia developed.
1	Not taken	11% (1072)	3 months
5	"	6% (543)	1-2 "
6	2% (253)	10% (1475)	4-5 "
7	0	19% (1387)	1 month
8	0	7% (505)	5 months
15	1% (101)	{ 3% (529) 5% (645)	1 month 7 months
16	0	4% (268)	10-11 "
17	2% (248)	5% (685)	2-3 "
18	3% (150)	8% (824)	3 "
19	1% (91)	8% (832)	2 weeks
22	6% (348)	18% (1548)	3 months

The figures in brackets represent the absolute number of eosinophil cells per cubic millimetre.

(1948) cases the percentage of those who showed eosinophilia was about the same as in the present series, and in those reported by Davies and Lennox (1946), 52 per cent. It ranges from 5 to 25 per cent. in the differential blood count. Davies and Lennox showed clearly that the eosinophilia is not incidental, but dependent on the ingestion of the tridione. When administration of the drug was discontinued the number of eosinophil cells fell. On recommencement of the administration their number rose again usually to its former level. In the present series this was not tested. In a number of those who showed eosinophilia tridione had to be discontinued when the drug was temporarily not available, and the results are shown in Table V.

In the first 24 cases of this series the stools of all patients showing eosinophilia were examined. Ova of *Oxyuris vermicularis* were found in all of them in a single test. The stools of the other patients without eosinophilia were

TABLE V.

Number of case.	Duration of treatment.	Eosinophilia at the end of treatment.	Eosinophils after withdrawal of tridione.	Eosinophils after recommencement of treatment.
1	5 months	11% (1072)	3% (174)	9% (598)
5	2-3 "	6% (543)	2% (192)	3% (354)
8	5 "	7% (591)	3% (195)	3% (270)
17	5 "	5% (644)	1% (96)	later 8% (568) 4% (482)
18	4 "	8% (824)	2% (240)	5% (360)

tested, some of them on several occasions, but no helminthic parasites were found. Since, except in one case, which gave a history of asthma of unknown origin, no other findings were brought to light which could in any way explain the eosinophilia, the following course was taken. The patients were treated with gentian violet for three days, followed by a dose of Epsom salts, and their blood count was repeated after the completion of this treatment. Tridione treatment was continued throughout. The results are shown in Table VI.

TABLE VI.

Number of case.	Eosinophil cells before treatment with tridione.	Eosinophil cells before antihelminthic treatment.	Eosinophils shortly after antihelminthic treatment.	Eosinophils several weeks or months after antihelminthic treatment.
1	Not taken	5% (515)	4% (84)	..
6	2% (253)	7% (857)	0	3-5% (350)
7	0	12% (1392)	9% (684)	..
8	0	8% (560)	4% (280)	5-8% (480)
18	3% (150)	7% (588)	2% (146)	..
19	1% (91)	8% (832)	0	3% (225)
22	6% (348)	18% (1728)	3-5% (560)	..

The antihelminthic treatment consisted of Gentian violet gr. i-iiij *t.d.s.*, according to the age of the patient. This was followed by one dose of magnesium sulphate.

With due regard to the small number of patients, these data seem to allow the following conclusions:

(1) The patients who show an eosinophilia when treated with tridione are also those who are infested with helminths.

(2) They do not show an eosinophilia before tridione is administered. Although no stool tests were taken before this treatment was started, it is most likely that the infestation had existed before. In other words, it is unlikely that all these patients have become infested as soon as treatment with tridione was commenced. Their blood count therefore shows that they were not generally sensitized to the helminths which inhabited their intestinal tract.

(3) When they began to take tridione they showed signs of sensitization; not to the drugs alone nor to the helminths alone, but only to both simultaneously. The tridione, therefore, appears to sensitize the organism to the previously existing infestation with intestinal parasites. The question arises as to whether the other side-effects of tridione therapy are in any way connected with the activation of the helminthic keratins by the drug.

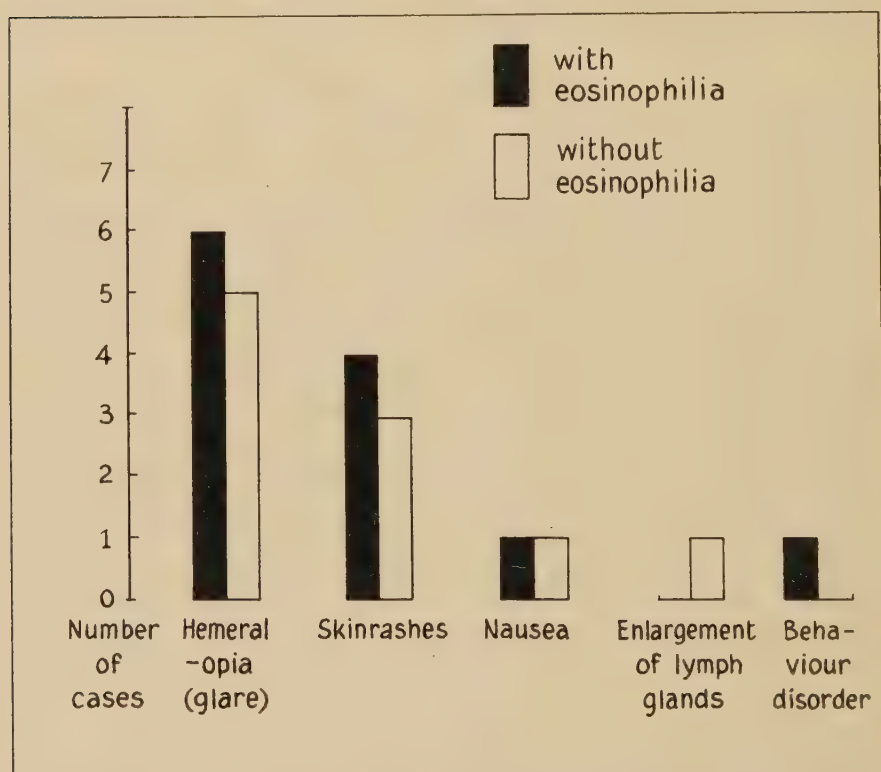
Table VII shows these side-effects in this series of patients, who for this purpose are divided into two groups—those with, and those without eosinophilia. There are neither qualitative differences in the sense that one particular effect would appear in the one and not in the other group. Nor are there quantitative differences in the sense that more ill effects are produced in one group than in the other. The commonly observed side-effects of tridione, therefore, correlate in no way with eosinophilia.

The relationship between neutropenia and the eosinophilia in the series by Davies and Lennox (1946) was as follows: Eosinophilia has not been confined to the group having neutropenia, although the average percentage for this group is 6.2, compared with 3.8 for the entire series. The present group of patients is too small to allow for statistical investigation. We found a slight transitory increase in the W.B.C. during the first 3 to 10 months in all our patients. This leucocytosis was not commented on by Davies and Lennox, but was observed by Hall (1948) during the first 3 months of treatment. In this series the group with eosinophilia showed differences in the differential cell count from the group without eosinophilia. In the first group the increase of W.B.C. was mainly due to lymphocytes. The neutrophil polymorphonuclear cells actually fell in number as soon as treatment was begun. This was

not so in the control group, where all cells increased in number. These facts would have to be confirmed in a larger series of cases.

The important question is whether this transient granulocytopenia is the precursor of the agranulocytosis found in a few patients. From an analysis of the cases in the literature this question cannot be answered, mainly because the necessary investigations had not been carried out. The interesting findings in the case described by Mackay and Gottstein (1946) are not conclusive

TABLE VII.



(Young, 1949). An investigation of this question would in any event be useful. If the mild transient form is a condition *sui generis* it is harmless and does not require treatment. In that case frequent blood examinations of the patient while under treatment do not seem to be necessary. If it is a precursor of the severe agranulocytosis, the connection with the changes due to allergy may open an avenue to treatment and prevention. It would make this powerful and valuable therapeutic agent, tridione, safer for clinical use.

SUMMARY.

1. Fifty cases of various types of epilepsy were treated with tridione, with or without other anticonvulsants.
2. The best effect was achieved in cases of *petit mal* either occurring alone

or together with other types of attack. The 3 c/sec. W.S. in the E.E.G. is not a *sine qua non* for successful treatment.

3. Major seizures occurring in addition to *petit mal* do not contra-indicate the use of tridione. They can be suppressed by adding epanutin or phenobarbitone to the tridione.

4. Some of the adverse effects have been discussed.

5. Eosinophilia was observed in 60 per cent. of the patients. This seems to be dependent on the presence of a helminthic infestation, but occurs only if tridione is taken at the same time.

6. The possible implications of this finding for the blood changes in general are discussed.

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DESOXYCORTONE ACETATE AND ASCORBIC ACID IN THE TREATMENT OF SCHIZOPHRENIA.

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DURING recent years there has been a revival of interest in the possible role of the adrenal cortex in the pathophysiology of schizophrenia.

There is now considerable evidence indicating a relative hypo-activity of adrenal cortical function in schizophrenia and a lower reactivity than normal subjects of the adrenal cortex to various forms of stress (Freeman *et al.*, 1944; Hoagland *et al.*, 1946; Pincus and Elmadjian, 1946; Pincus *et al.*, 1949). Increased adrenal cortical activity has been shown to occur in electroconvulsive therapy, electronarcosis and insulin therapy. Direct evidence of increased adrenal cortical activity during electroconvulsive therapy was obtained by Ashby (1949) who found a brisk outpouring of cortical steroids during the first few days of treatment. Similarly measurements of lymphopenia and eosinopenia has given evidence of enhanced adrenal cortical activity during the above methods of treatment (Mikkelsen and Hutchins, 1948; Rees, 1949a; Parson *et al.*, 1949).

It is concluded by Hemphill and Reiss (1942) and Hoagland *et al.* (1949) that electroconvulsive therapy mobilizes adrenocorticotrophic hormone (ACTH) endogenously resulting in increased formation of adrenocortical hormones.

While there is considerable evidence of increased adrenal cortical activity occurring concomitantly during the application of various physical methods of physical treatment, it is not yet known whether it is partly or wholly the therapeutic agent.

Further interest has been stimulated in adrenal cortical function in mental illness by the work of Hans Selye (1937, 1942, 1946, 1949), emphasizing the importance of the adrenal cortex in adaptation to stress, and the dramatic discovery by Hench *et al.* (1949) that cortisone was therapeutically valuable in rheumatoid arthritis.

Carlisle (1950) reported that a definite improvement in mental attitude of patients receiving cortisone usually occurs, often with acceleration of the alpha waves in the electroencephalogram, whereas in rare instances pre-existent

or latent mental disorder such as schizophrenia seems to have been intensified or precipitated.

In view of the fact that cortisone is virtually unobtainable and ACTH is in very short supply, substitutive methods were sought.

Lewin and Wassen (1949) claimed that desoxycortone acetate (D.C.A.) given with ascorbic acid produced beneficial results in rheumatoid arthritis. It was assumed that ascorbic acid acted on desoxycortone to produce cortisone or other active anti-rheumatic substances. Hallberg (1950) considers the interaction to be oxidation of D.C.A., whereas Landsberg (1950) maintains that the action is one of reduction. Some workers have confirmed the results of Lewin and Wassen (Lavery and Loxton, 1949 and 1950), Fox (1949), but the investigations of many workers did not support their claims (Kellgren, 1949; Hartfall and Harris, 1949; Lloyd and Starer, 1949; Currie and Weil, 1950; Spies *et al.*, 1949; Bywaters *et al.*, 1950).

Cranswick and Hall (1950) treated a series of psychiatric patients with D.C.A., and ascorbic acid and found a fall in eosinophile count, a change in the urinary uric acid/creatinin ratio and regarded this as suggesting the production of a cortisone-like substance. They found that some patients improved and pointed out the need for further investigation.

This paper describes a controlled investigation into the value of D.C.A. and ascorbic acid in the treatment of schizophrenia.

METHOD.

The possibility that the mere procedure of giving a series of injections might have therapeutic effects by suggestion or otherwise, makes it particularly important to institute a control series of patients receiving inert injections by a similar procedure. The control and treated groups should participate equally in the general hospital regime and should correspond in age and sex distribution, mental status and tendency to spontaneous recovery.

The experimental group consists of 28 schizophrenics comprising 14 pairs of patients matched for age, sex, mental state, duration of illness and previous treatment. The matching was carried out after a detailed assessment of clinical status, utilizing an item sheet of some 300 items relating to history, clinical state and prognosis. Mental status was rated in terms of components in accordance with the method of Rees (1949*b*) whereby such features as introversion, intellectual or emotional disconnection, paranoid disposition, etc., are rated on a seven-point scale according to severity. Data collected and recorded in this way enabled the matching of patients to be carried out readily and effectively.

An analysis of salient features is shown in Table I.

An additional technique was used to record clinical progress. This was a modification of the psychiatric rating scale of the Worcester State Hospital and involved rating each patient on some 15 traits in terms of deviation from the patient's previous behaviour and personality. The sum total of the scores on the rating scale gives an abnormality index which computed before, during and after treatment, provides a graphic and quantitative expression of behaviour

TABLE I.—*Item Analysis.*

<i>Sex distribution.</i>	Per cent.	<i>Aetiology—cont..</i>	Per cent.
Male	57	Exogenous factors contri-	
Female	43	buting	18
		Mainly endogenous	54
<i>Age.</i>		<i>Mental status.</i>	
15-19	7	<i>Introversion.</i>	
20-29	32	High (4+)	65
30-39	36	Low (0-2)	35
40-49	25		
<i>Family history.</i>		<i>Intellectual disconnection rating.</i>	
Negative	83	High (4+)	73
Psychosis	13	Low (0-2)	18
Neurosis	4		
<i>Previous mental health.</i>		<i>Emotional disconnection rating.</i>	
Normal	50	High (4+)	39
Definite illness	13	Low (0-2)	45
<i>Personality.</i>		<i>Conduct disconnection.</i>	
Stable	43	High (4+)	37
Very unstable and illadjusted	39	Low (0-2)	45
Broad interests	5	<i>Paranoid disposition.</i>	
Very touchy and suspicious .	27	High (4+)	14
Very schizoid	23	Low (0-2)	59
Cyclothymic	9		
<i>Duration of illness.</i>		<i>Depression rating.</i>	
Less than 1 year	28	(2+)	9
1-3 years	12	<i>Excitement (all ratings)</i>	4.5
Over 3 years	60		
<i>Onset of illness.</i>		<i>Intelligence rating.</i>	
Sudden	28	Below average	13
Prodromata then acute	7	Average	78
Gradual	65	Above average	9
<i>Aetiology.</i>		<i>Diagnostic subtype.</i>	
Psychological causes impor-		Simple and hebephrenic	72
tant	18	Catatonic	14
		Paranoid	14

changes during and after treatment. The item sheet and rating scale were completed by one of us (L.R.) and the matching of pairs carried out in consultation.

One member of the pair was given an intramuscular injection of 5 mg. D.C.A. followed by an intravenous injection of 1 gm. ascorbic acid. The other member was given, for control purposes, an intramuscular injection of arachis oil and an injection of saline intravenously in similar quantities, and in precisely the same way. The treatment and control procedure was given thrice weekly for 4 weeks. To eliminate the possibility of subjective bias, assessment of clinical state and behaviour during and after the treatment was carried out by the assessor without knowing which patient had received the active injections and which was the control.

All patients participated in a full regime of occupational and recreational therapy.

RESULTS.

No significant changes were noted in clinical state or behaviour of patients receiving D.C.A. and ascorbic acid either from observation in the wards by medical and nursing staff, or by the more objective method of the Psychiatric Rating Scale. The only person in the series showing any significant change was a member of the control group, an early schizophrenic who improved during the period of administration of the inert injections.

DISCUSSION.

The results are unequivocal and provide no evidence that D.C.A. and ascorbic acid when given by the technique described had any therapeutic effect on the group of schizophrenics studied.

The group contains a number of patients with a long duration of illness and other unfavourable prognostic features, and it might be held that these patients would be unlikely to respond to any treatment. It is therefore particularly noteworthy that no improvement occurred in patients with an illness of less than one year's duration, and other favourable prognostic features.

The need for caution in attributing improvement accompanying or following therapeutic trial to the particular treatment under investigation, is indicated by the recovery of one of the patients whilst receiving the course of inert injections. This might be due to coincidence with spontaneous recovery, or possibly suggestion may have had therapeutic effects.

The investigation throws no light on the possibility that other products of adrenal cortical activity may be therapeutically valuable in schizophrenia. Hoagland (1950) reporting the results obtained by giving ACTH to a small group of schizophrenics found improvement in one case only out of five, and the improvement ceased when the ACTH was discontinued. It is possible that the therapeutic effects of the various shock therapies are not due entirely to release of endogenous ACTH. Further research is urgently needed to ascertain the effects of adrenal cortical products on functioning of nervous tissue and whether any particular product of adrenal cortical activity is responsible for the beneficial effects of shock methods of treatment.

SUMMARY.

1. The experimental population of the study consists of 28 schizophrenics, comprising 14 pairs of patients matched, after detailed clinical analysis, for age, sex, mental state, duration of illness and previous treatment.

2. One member of the pair was given thrice weekly injections of 5 mg. of desoxycortone acetate (oily) and 1 grm. of ascorbic acid intravenously (aqueous) and the other member serving as a control was given a similar quantity of arachis oil intramuscularly and saline intravenously. Both groups participated equally in a full regime of occupational and recreational therapy.

3. Each patient was assessed before, during and after the course of injections by means of a psychiatric rating scale. In order to avoid the possibility of subjective bias, the assessments were made without knowing which patient had received the D.C.A., and ascorbic acid and which was the control.

4. No significant changes were noted either on clinical observation by doctors or nurses, and no significant improvement was noted in the abnormality ratings given by the psychiatric rating scale.

5. The investigation, therefore, provides no evidence to suggest that desoxycortone acetate and ascorbic acid given in the manner described has any material beneficial therapeutic results in schizophrenia.

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AN ACCOUNT OF E.C.T. GIVEN TO A PATIENT WITH A TANTALUM PLATE IN HIS SKULL.

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THIS case has been recorded because it seems to be the first in which E.C.T. has been given to a patient with a skull defect repaired by means of a large metal plate. It is also of interest because there was some doubt about the diagnosis, although this was resolved by the response to treatment.

CASE HISTORY.

The patient, an unmarried Englishman, aged 30, was first seen in Dr. Curran's clinic at the Psychiatric Out-Patient Department, St. George's Hospital, in November, 1948. He complained of "a feeling of inferiority in everything," which had caused him to give up his job as an insurance clerk in September, 1948.

History of Present Illness.

This was obtained from the patient and all important details verified by his mother, his employers, and by consulting his Service and pension documents.

Early in March, 1945, during the fighting in Holland, the patient was wounded in the left fronto-parietal region by a bullet from his own Sten gun, which discharged accidentally. There was no question of attempted suicide. He had a retrograde amnesia of a few minutes and a post-traumatic one of many hours. The exact details of the brain damage caused by this wound were not recorded, but his notes state that a large skull defect was repaired with a tantalum plate in the Head Injuries Unit at Oxford. A series of psychological tests done in May, 1945, suggested that his judgment was mildly impaired.

In August, 1945, shortly after leaving hospital he drank heavily and had an epileptic fit. After this he returned to work and did fairly well until mid-1946, when he became depressed and apathetic for about 2 months and stopped work for some weeks. In the summer of 1947 these symptoms recurred, but disappeared again after a holiday. Early in 1948 he was given a rise in pay, which his firm said was deserved. In July, 1948, while on holiday, he had tonsillitis, which persisted for some weeks, and with it he became increasingly depressed.

He stopped work in September, and resigned from his job in October because he believed, quite incorrectly, that he was about to be sacked for inefficiency.

From September until he was seen at out-patients he remained at home doing nothing.

He was admitted to hospital for investigation and treatment. A provisional diagnosis had been made of a depressive reaction to organic mental impairment following severe head injury.

Personal History.

The patient is the second of four brothers. His father, dead for some years, the three other brothers and his paternal grandfather were notorious for their moodiness, which was a recognized family failing not shared by the patient. A paternal uncle is a periodic drinker.

He seems to have had a happy and uneventful childhood. He failed School Certificate, and went into his present work as an insurance clerk when aged 17. In work, as in play, he was reliable without ever shining. He was a Territorial, and

in 1939 went into the Army as a private. He adjusted well and remained a private until he was invalided in 1945 with a 50 per cent. wound pension. He fought in France in the infantry from shortly after D Day onwards.

- 1 He has enjoyed good health.
- He denied sexual difficulties.
- He is a moderate drinker and smoker.
- His weight has been steady.



FIG. 1.—Photograph of patient to illustrate the excellent surgical repair of gunshot wound of skull—sustained in March, 1945, and operated on at the Head Injuries Unit, Oxford.

Mental Examination.

Appearance.—He was neatly and tidily dressed, but was harassed and drawn, and looked miserable.

Activity.—He stated that he lacked energy and initiative.

Thought.—He said he was indecisive, could not concentrate or write letters, and he felt that his mind was empty.

Memory.—He showed no obvious defect on testing. He retained 8 digits forward and 5 back, did Babcock sentence (23) in three attempts, and in Serial Sevens made one error, taking 45 seconds on the test.

Mood.—He described himself as depressed. He admitted to suicidal thoughts and saw no hope for the future.

Sleep.—For two months prior to admission he had been waking early and had difficulty in getting off to sleep.

Delusions, etc. —He was very self-reproachful and had some ideas of reference, feeling that people talked about him unfavourably because he was so quiet.

Detailed psychological testing was done by Mrs. A. Petrie at St. George's Hospital; Col. B. Ungersson of the War Office was kind enough to lend the results of testing before the patient was wounded, when in a series of verbal and non-verbal tests he was placed consistently in the first 10 per cent. of the population.



FIG. 2.—X-ray photograph of skull (postero-anterior view) to show the size of the tantalum plate. The patient's picture is to be seen in Fig. 1.

Four years after the injury he was in the same first 10 per cent. He showed no evidence of deterioration in numerous tests except for a loss in the finer distinctions of language similar to that seen in post-leucotomy patients (Petrie, 1949).

Physical Examination.

The patient was 5 ft. 8 in. high and weighed 11 st. 12 lb. He was of pyknic build, with deep body cavities. All systems were examined but no abnormality found. The photograph shows the excellent results obtained by the surgical repair of his cerebral injury. While he was in the ward another patient (a doctor), who was in the next bed, was unable to say where the scarring was because he

had never noticed it during the week in which they occupied the same room. W.R. and Kahn were negative. Chest X-ray was normal. Skull X-ray plates (reproduced here by the courtesy of Dr. James Bull of the Neuro-Radiological Department of St. George's Hospital) showed a large metal plate in the left fronto-parietal region and a retained metallic fragment in the vault near the right border of the plate. Otherwise his skull was normal.

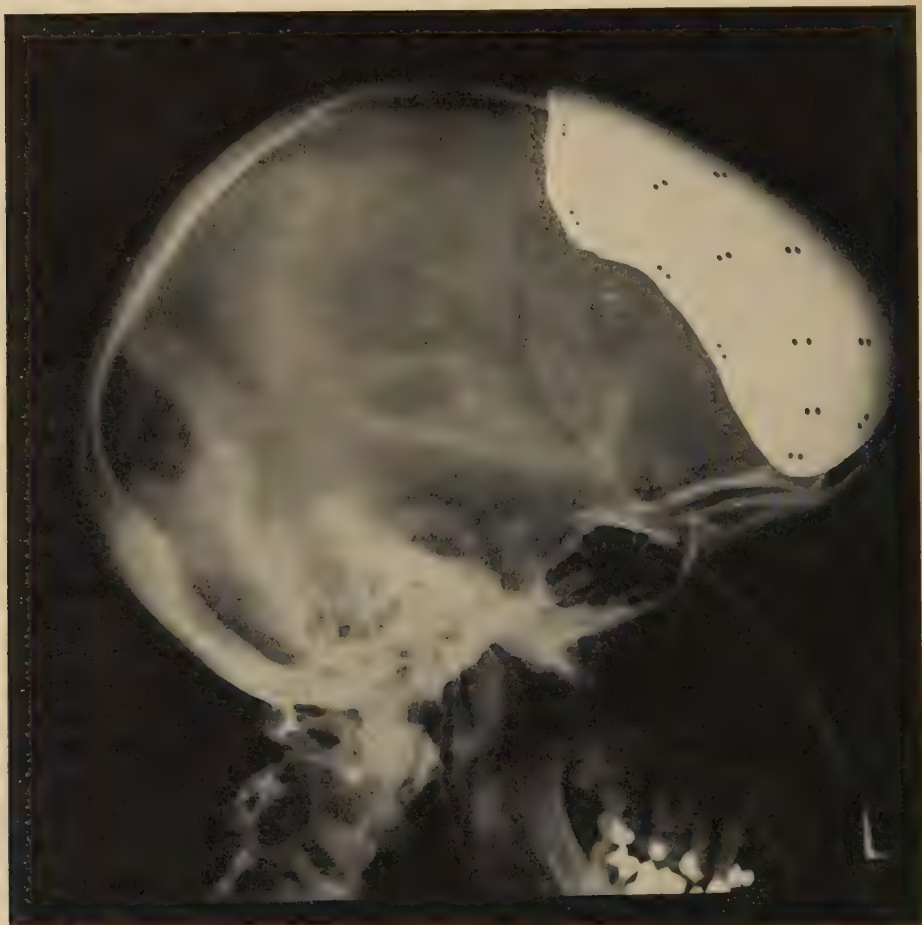


FIG. 3.—X-ray photograph of skull—lateral view.

Dr. Denis Williams reported on his electro-encephalogram done on 31 December, 1948: "Otherwise normal records showed symmetrical high voltage 6-a-second waves which represented epileptic discharges. The suppression of activity on the left side was, I think, more extensive than could be explained by the plate, and raises the possibility of great loss of brain tissue." A further E.E.G. done after he had been treated with convulsion therapy on 9.ii.49 showed more generalized abnormality, but Dr. Williams considered this might have been caused by changes in the E.E.G. instrument.

Diagnosis.

Even at the first interview this patient's ability to remember 8 digits forward and 5 back and his success in the Serial Sevens raised doubts about the provisional diagnosis. After further investigation it was considered that he was suffering

from a depressive state of the anergic type, precipitated by head injury in a man with a strong history of cyclothymia for at least three generations on the male side.



FIG. 4.—X-ray photograph of skull (Towne's view).

TREATMENT.

It was a new experience to give E.C.T. to a man with a metal plate in his head, and there was some doubt as to what would happen.

Tantalum is a metal with an atomic weight of 181.88, an atomic number of 73. It is of the rare earth group whose melting-point is 2,275° C. It is very inert chemically, and because it causes little tissue reaction is used in repairing skulls where there has been extensive brain damage.

Colleagues in various departments suggested alarming possibilities, which included some alteration to the type of fit, over-heating the tantalum plate

and so, as it were, cooking the brain ; bending the plate during the fit, and also depositing tantalum around it electrolytically. None of these seemed sufficiently likely to contra-indicate treatment, and there are no references to them in the literature. The E.C.T. results have been tabulated below :

Number of fit.	Date.	Hours.	Joules.	Cyanosis.	Remarks.
1	11.i.49	1345	17	++	Excessive reaction.
2	13.i.49	0935	12	++	Very major convulsion.
3	15.i.49	1000	10	++	} Twitching movements of hands and feet, mouthing gag +.
4	17.i.49	1315	10	++	
5	21.i.49	1135	10	++	
6	24.i.49	1010	10	++	
7	28.i.49	1330	10	++	Major fit, bilateral finger twitching.

On 1.ii.49 the patient agreed that he was now recovered and paid a bet which he had made that treatment would fail. He was sleeping without sedation and described himself as being " back to normal. A hundred per cent. better." The skull X-ray on 8.ii.49 showed that the plate had not moved.

On 9.ii.49 he left the hospital for three weeks on a holiday which he had arranged for himself. He has been seen at irregular intervals over the last year and letters received from him. In spite of losing his job because of the illness he has remained optimistic and cheerful. When he left hospital he hoped that his firm would reinstate him ; they did not do so. He obtained another job in similar work, and when last heard of in September, 1949, had been working for 8 months and considered himself completely recovered.

Shortly before this paper was completed in September, 1950, the patient was seen again. He had remained well until the middle of the year, when a further depression had set in, characterised especially by irritability and anergia. He had had about 13 spontaneous fits during the last 12 months. He was, as before, very reluctant to have treatment, but eventually agreed to come into hospital and had 7 E.C.T. with complete recovery. Dr. Denis Williams saw him about the fits, and since being on a more effective anti-convulsant he has had no more. E.C.T. proceeded without incident except that a smaller current was needed.

DISCUSSION.

There are many reports in the literature of E.C.T. being given in unusual cases ; the very young, the aged and infirm, and those far gone in pregnancy, have all been successfully treated in this way at one time or another. Cook (1949), from his wide experience of the subject, has never heard of E.C.T. being given to a patient with a metal plate in his head, nor has an extensive search of the literature yielded any other cases. Treatment involved risks, but the result has been good enough to justify them. There will not be many cases like this one ; but with the increase of extensive brain surgery it is possible that from time to time other patients will be seen for whom E.C.T. might be

withheld because of doubts about its safety, when, if given, it would produce speedy relief of symptoms and return to work. In this case it is clear that the patient has suffered little impairment from his extensive loss of brain tissue, so far as can be ascertained by tests and his ability to work.

SUMMARY.

A depressive state following extensive head injury is described in which the skull had been repaired with a large tantalum plate. The problems of treatment are discussed and the results of E.C.T. given. The writer believes that the case is unique.

ACKNOWLEDGMENTS.

I wish to thank Dr. Desmond Curran for permission to publish this case and his advice and help on writing this paper, and also thank Sir Paul Mallinson and Dr. Maurice Partridge for their criticism and interest.

The patient was kind enough to allow his photograph to be published.

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THREE ASPECTS OF EGO-ORGANIZATION IN RELATION TO ETHER ABREACTION THERAPY.

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IN this paper I propose to describe three varieties of behaviour of patients under treatment by means of ether abreaction.

STAGE I: SIMPLE REMINISCENCE.

When a patient is given an anaesthetic there is an initial stage in which there is no apparent alteration of reality function. This can best be described in colloquial terms; the patient feels that "this is me lying on this couch talking to you, doctor." We can dispose of what follows in the average patient by saying that presently a variety of physical sensations supervene, the conscious state disappears and presently the patient becomes, as we would say, anaesthetised. It is interesting to observe, however, that there is a stage coinciding with the loss of consciousness at which the patient makes semi-purposive movements, giving the impression that mind is still operative, that is to say, the organism is still acting more or less as a whole. Moreover, if the patient is allowed to emerge from a session during which anaesthesia has just been produced to a level which would be consistent with minor surgery, then, upon waking, the patient will often appear somewhat bewildered and perplexed in relation to experience which he expresses in such terms as "where have I been? What have I been saying?" Or it may be he will say something like this: "Good heavens! I was back at school, Doctor." Such a recapitulation of mental experience may or may not be accompanied by an emotional reaction, but when this occurs the emotion is usually one of sadness. Fear and (more rarely) anger are also encountered. Laughter is not a characteristic accompaniment.

This stage may be utilized for the purpose of aiding reminiscence in psychiatric procedures.

STAGE II: CONTROLLED AND DIRECTED REVERIE.

To provoke this stage the operator must have some knowledge of the events he is going to deal with and, ideally, should then assume an exhortatory tone of voice and say something like the following: "Now there you are (doing such and such a thing)." The majority presently pass into a stage of dissociation or reverie. It is as if there were two selves:

(a) One lying on the couch talking to the operator.

(b) The other taking part quite vividly in the re-enacted reminiscence or reverie.

Where the re-enacted incident does not possess too strong an affective charge and in the absence of other features presently to be mentioned, the patient beholds the re-enacted material as a very vivid visual drama, as if that which was watching the scene was above, generally behind, and usually somewhat to one side of the visual drama the person on the couch is describing. If the event depicted possesses strong affective significance ; if a patient is suffering from obsessional forms of neurosis ; with most hysterics ; and most strikingly of all with patients in whom there has been a strong traumatic experience associated with subsequent amnesia ; the patient on the couch gives a commentary as if he were verbalising his own thoughts which had taken place at the time of the original incident. A clear distinction can be made between this verbal commentary and the more vivid and dramatic exclamations which punctuate this verbal commentary, and which are presumably the words of the original experience. This has been described by many authors dealing with abreactive techniques and is not peculiar to ether.

In the following excerpt of a session where the patient is re-enacting a battle scene in which a comrade was killed, the soliloquy is in ordinary print, and the original words are in large print.

" . . . there is some awful stuff coming over—LOOK OUT BILL—God, that was a near miss . . . we will have to get out of here—IT'S NO USE SERGEANT, HE'S DEAD."

Working through such an incident it is as if the patient were rapidly alternating between a complete dissociation in which part of him is as good as back to the time and place where the events originally occurred, and the present entity " watching " these events. A third " part " is on the couch. I can designate our entities so far described as follows :

(a) Me lying on the couch talking to you, doctor " (doctor-patient relationship).

(b) " Myself " taking part in the re-enacted episode—(no relationship with doctor or present time).

(c) " That which is watching " ; not corporeal but nearly always above, behind and slightly to one side of that which is being watched. (Doctor's voice—watcher relationship plus watcher—re-enacted episode relation.)

When an experimental subject tries to discuss the relationship between the " watcher " and " me lying on this couch talking to you, doctor," and " myself (taking part in the dream)," it seems as if there is a very close connection between the watcher and that which speaks (or might we say the executive " I " ?).

STAGE III : HYPNAGOGIE.

In the case of a significant number of patients, but by no means the majority, a third stage is encountered as follows : Having stopped the ether and roused a patient who has just been describing his reverie along the lines delineated under Stage II, he or she will sit up and say " Good heavens ! where have I been ? . . . I was at school," or it may be I was here or there ; and this is the curious thing, the events described at this point are quite different in

time and place from that which they have been talking about a minute previously. Metaphorically speaking, it is as if the patient had just been in a room which had two doorways, one opening into the real world, "me lying on this couch talking to you, doctor," and the other opening into a room which contains the mental furniture which is the subject of this third stage.

In this stage the figures in the drama are usually of slightly less than normal size. Colouring is present which differs from normal colouring in emphasis; it may be richer and vitalized, reminiscent for instance of the paintings of Georges Rouault. The patient's description tends to be about dominant colours, which are most frequently orange, yellow, then green and occasionally blue. Red is very rarely encountered. A quite common expression for the patient to use is "everything is yellow, bathed in glorious sunlight."

There is always a symbolic link between the second and third stage. The following is an example :

A soldier was referred with a severe stammer and blindness which had come on following the explosion of a hand grenade. There was no amnesia. Under ether the whole of the incident was re-enacted with vivid reality, but as he woke up he said words to this effect : " Good heavens ! I have been in the movies," and when asked to describe this (third stage effect) he proceeded to describe how on his embarkation leave he had attended the film " Gone with the Wind," in which it will be remembered there is a rather gruesome casualty clearing station scene in which one of the characters of the play is blinded. Now this particular patient, as a boy, had suffered from a squint, for which he had been successfully operated. He had attended the movies with a friend and, after his visit to the movies, had proposed to her and the next day had sailed for duty overseas. It is clear, therefore, that the affective charge of the hand grenade experience threatening him with loss of vision (he had been " blinded " by the flash) had got linked up with the affective charge associated with his embarkation leave experience, for which the movie event had been the symbol. This, in turn, was related to the earlier worry about losing his sight. As a rule the third stage is not utilized for therapy except as a link which leads to the fourth stage.

STAGE IV : DREAM-LIKE PHASE.

The fourth stage resembles ordinary dreaming, and compounds in condensed form items from adult and infantile experience. Most patients, and indeed experimental subjects, are temporarily disturbed, sometimes to a very severe degree, if one takes them through this fourth stage. They become afraid and bewildered in a manner reminiscent of acute schizophrenia. I have formed the impression that the extent to which they are disturbed depends on their real situation and also on their mental type. Patients differ markedly in their ability to enter the fourth stage. Taking it by and large, I associate spontaneous entry into this fourth stage with the more psychotic fringe of my case material. On the other hand, some experimental volunteer subjects also can enter this stage with ease. The schizoid hysteric who has general psychopathic traits very frequently exhibits this fourth stage.

The figures which are described in this fourth stage also contain colour and are vivid and defined, though this may occasionally have caricature-like qualities.

The emotional context of this stage is described as being diffuse, and not specific to the items of experience. This is also true of Stage III, but very different from Stage II, in which there is specific emotional context comparable to normal experience.

This evidence appears to suggest that there may be at least three related ego systems which are dependent one on the other, and that a fourth system may relate to that which I have called "the watcher." I have occasionally thought that the phenomenon of the "watcher" links up in some manner with the problem of the auditory hallucination.

The following is a verbatim account, taken down at the time of the interview by a stenographer, which illustrates the main varieties of phenomena which have been referred to in the text.

The subject was a volunteer control subject selected from a group of non-medical students. She had absolutely no knowledge of the technique, and had not attended any lecture on psychotherapy.

Very special care was taken to ensure as far as possible that the subject was not unwittingly producing the phenomena we were endeavouring to observe. All sessions were conducted with a second trained observer to check on this. This subject, so it eventually transpired, was in the throes of a very minor emotional problem. In addition she bore a surgical scar on her neck, the result of childhood injury. At the time of the experiment she was concerned about a particular pupil's progress. She was asked to discuss the events of the previous week, included within which was a visit to the home of her pupil. This episode was selected for ether abreaction. She was placed on the couch and told to visualize her going to the pupil's house :

Doctor : You can see yourself quite clearly . . . there you are getting off the tram and going into the shop.

P. : I am walking in the door . . . there is no one in the shop. I had better press the bell . . . I am teaching Ted; could I speak to his father? I will come back later. . . . Oh, good morning! I'm Ted's teacher . . . is Ted happy?

Doctor : Do you picture yourself or do you seem to be there?

P. : I picture myself . . . there is the bell. I can see myself in a green coat.

D. : Where are you in relation to yourself in the shop?

P. : I am standing behind myself—slightly above—slightly to the left side.

D. : You can see "myself" in a green coat, what is it that is seeing "myself"?

P. : It seems to be me "here now" that is watching.

D. : Has it bodily attributes?

P. : No. I don't think so.

D. : And yet it is the same as "me here."

P. : Yes, there are three people—"me lying on the couch" talking to you," "me in the shop" and "me watching."

D. : What are the physical attributes of the "watcher"?

P. : Nebulous.

D. : Where is "me" . . . "talking to the doctor"?

P. : Mostly in my head.

Ether was recommenced and the experiment reproduced. Then ether stopped.

Doctor : Where have you been?

P. : I suppose I was in the shop.

D. : Were you really in the shop ?

P. : Yes, but I was conscious of this.

D. : Which was the more real ?

P. : In the shop.

D. : Have you been anywhere else ?

(This part illustrates the first and second stages. The subject of the experiment had no prior knowledge of the phenomena involved in the experiment.)

P. : Except at one stage I seemed to be outside Shore School.

More ether given and subject taken to Shore School. The third stage emerges.

D. : There you are. Ted is in the room.

P. : I can see the teacher at the desk. . . . Ted is standing up. . . . Hallo, Ted ! what have you been doing ? . . . I haven't seen you since last Friday—(patient very restless)—I like this one. I will paste it in for you (patient re-enacting in reverie a paste-book exercise).

By this time the patient was mildly intoxicated but easily rousable. She was left a second time and asked where she had been.

D. : Have you been anywhere else beside Shore School ?

P. : That's funny . . . I seem to have been outside our old house in Shore. (The fourth stage emerges.)

More ether was given and patient was " put " in front of the family house where she had spent her childhood. She recounted how she had cut herself with a knife whilst having dinner one day and there were carrots on the table. She was prompted to live through this childhood traumatic experience. As she emerged from the fourth stage with the discontinuance of the ether she appeared bewildered and disturbed, but recovered in the course of approximately fifteen minutes. She then remarked spontaneously that she had noticed some carrots in the green-grocer's shop of the second stage reminiscence.

This subject was then asked to return in four weeks and meanwhile epitomize her experience. I would reiterate that this subject was a non-medical university graduate without any knowledge of my technique. This is her story (author's comments in parenthesis) :

" I can differentiate three stages of experience under ether, but I do not differentiate qualitatively between them. First there is " me " lying on the couch, then the " watcher " situation, and finally the stage I am actually " in "—viz. the recalled situation. They seem to be progressive states. . . . As far as emotional reactions are concerned I can distinguish two classes :

" (a) In the situation where I was placed into a remembered experience there was no particular emotional feeling except what arose from the respective conversations, except this was perhaps more intense under the ether (second stage).

" (b) When I was placed into the situation in front of my old home and where you were clearly with your dreams there was a general emotional tone covering the whole experience, more diffuse than (a) and more difficult to analyse. (In this instance the subject made no distinction between the second and third stage.)

" I feel that the watcher did not do any of the speaking, and was just there and did not seem to have any relationship to me. I find it hard to believe that I did not remember the second incident (third stage), as I seem to have been there quite a long time. I can find no connection between the various incidents, but I now remember that when I was a year and ten months I had cut my neck while my mother and father were having dinner, and when thinking back to it it always seemed to me that there were carrots on the table. I had a definite feeling of relief when this connection was explained to me."

This subject produced typical material illustrating the four stages : (1) reminiscence, (2) reverie, (3) hypnagogie, (4) " dream." Recent experience, together with less recent experience and infantile experience, relived without being recalled by the operator. The " watcher " problem is also brought into clear outline.

The general purposes of this article have been to record my experience over the last few years in what appears to me scientifically verifiable samples,

and not to advance the therapeutic claims or push speculative theory beyond what is reasonable.

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A NOTE ON THE *a-b* RIDGE COUNT AND INTELLIGENCE.

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[Received 3 November, 1950.]

THE *a-b* ridge count, called the *a-b* count for short, is the number of epidermal ridges crossing or touching a fine straight line drawn joining the triradii *a* and *b* on the palm. The triradial point, or the radiant when the former is absent, is not included in the count. It was pointed out in a previous work (Fang, 1949) that, on the assumption that university students are more intelligent than the general population, there is a consistent increase of the mean *a-b* count with intelligence. The results of the present study seem to agree with this finding.

The study was based on the palm prints of the following samples :

1. University students—238 females and 80 males, believed to be mainly British by descent.

2. Non-specified types of mental defectives—36 idiots, 133 imbeciles and 35 morons, known to be British by descent. Specified types of defectives, such as mongoloid imbeciles, defectives due to birth injury or diseases, etc., were excluded.

The palm prints of the students are part of a collection made by Dr. Norman Ford Walker, of the University of Toronto, during the past some fifteen years, and those of the defectives are part of a collection made by Mr. A. Butler and myself at the Ontario Hospital School, Orillia, in the summer, 1950.

The results of this study are summarized in Table I. For convenience of comparison, some results obtained from the previous study are included. It is noted here that in the previous study the average of the *a-b* counts on the right and left hands of an individual was used, while in the present the total, instead of the average, was used. For instance, when the right hand has an *a-b* count of 42 and the left hand 44, the total 86 instead of the average 43 is used. The increase of mean count with intelligence and the agreement between the present and the earlier studies can be seen from the following analysis.

1. The mean count of students in Ontario-British population is 85.32 ridges, while that of students studied in England is 84.31. The mean difference of 1.01, with a standard error of 0.89, is probably due to sampling variation.

2. The mean count of the non-specified types of the Ontario-British defectives is 80.62 ridges, while that of defectives studied in England is 79.23.

* Holder of Canadian Red Cross Scholarship.

As the mean difference of 1.39 has a standard error of 0.90, it too can be ascribed to sampling variation. A consistent sex difference in the mean count, higher in females than in the males, is present in the three grades of Ontario-British defectives, though it was not observed in the corresponding English

TABLE I.—*The Mean a-b Counts and Percentage Frequencies of the Low Count Class in the University Students, General Population and Non-specified Types of Mental Defectives in Two Sets of Samples (One Studied in England and One in Ontario) mainly British by Descent.*

Sample.	Sex.	Number.	Mean s.d.	Per cent of 78.
<i>Students :</i>				
1. England	F.	78	85.04—11.2	20.5
	M.	126	83.50—9.8	23.0
	Av.	204	84.31—10.4	22.1
2. Ontario	F.	238	85.37—9.8	23.5
	M.	80	85.16—11.7	26.3
	Av.	318	85.32—10.3	24.2
<i>General Population :</i>				
1. England	F.	435	83.01—9.7	26.7
	M.	424	83.04—10.3	29.7
	Av.	859	83.03—10.1	28.3
<i>Mental Defectives :</i>				
1. England	F.	201	78.56—11.2	51.2
	M.	258	79.84—12.2	49.2
	Av.	459	79.23—11.8	50.1
2. Ontario :				
Idiots	F.	17	84.53—11.1	29.4
	M.	19	80.47—10.8	47.4
	Av.	36	82.50—10.9	39.0
Imbeciles	F.	56	81.43—12.3	37.5
	M.	77	78.58—9.1	52.0
	Av.	133	79.77—10.4	45.8
Morons	F.	15	84.27—10.7	40.0
	M.	20	80.85—8.1	35.0
	Av.	35	82.31—9.0	37.1
Total	F.	88	82.51—11.6	36.4
	M.	116	79.28—9.1	48.3
	Av.	204	80.62—10.2	43.1

sample. The mean count is slightly, though not significantly, higher in the idiots and morons than in the imbeciles.

3. The mean count of the general British population studied in England is 83.03 ridges. This is significantly lower than that of the Ontario-British students, but higher than that of Ontario-British defectives. The mean difference between the British population and Ontario-British students is -2.85 , with a standard error of 0.64 ; that between the general British population and Ontario-British defectives is 2.41 , with a standard error of 0.77 .

ACKNOWLEDGMENTS.

The palm prints of the mental defectives at Ontario Hospital School, Orillia, were collected, thanks to Dr. Ford Walker, through the kind co-operation of the superintendent, Dr. Montgomery, and his staff.

REFERENCE.

FANG, T. C. (1949), "A comparative study of the *a-b* ridge count on the palms of mental defectives and the general British population," *J. Ment. Sci.*, **95**, 401.

Part II.—Reviews.

Science : Its Method and Its Philosophy. By G. BURNISTON BROWN.
London : George Allan & Unwin, 1950. 15s.

This small book illustrates the difficulty of conveying to an educated public the philosophical basis of science. The author fully succeeds in three essays treating the life, work and historical background of some great scientific thinkers from Aristotle to J. S. Mill. These he introduces by a chapter on learning of animals giving a kind of phylogenesis of science ; and he makes his exit with a Dialogue in the style of Galileo that leaves most questions unanswered. In the two chapters on modern science itself, his anecdotal and sometimes facile exposition shows its weakness ; the result of pleasantly presented tit-bits of knowledge on the uninitiated seems to the reviewer very doubtful. Psychiatrists will especially enjoy the clear and readable chapter on "symbol situations," i.e. on words, definitions and the role of language in philosophy of science.

W. MAYER-GROSS.

Electroencephalography. By W. GREY WALTER, DENIS HILL, W. A. COBB, D. WHITTERIDGE, G. D. GREVILLE and M. E. HEPPENSTALL.
London : Macdonald, 1950. Pp. 438. Price 78s.

This excellent volume on a very difficult and technical subject is more than a text-book on electroencephalography—it is a study in the electrophysiology of the brain considered in its widest sense.

The information supplied covers a very wide ground and apart from the technical side of the E.E.G., which is covered most completely by Dr. Grey Walter, chapters are provided on physiology, biochemistry and pharmacology, before the reader is taken to the application of the E.E.G. in practice.

Chapters are provided on normal rhythms, on epilepsy, intracranial tumours, cerebral trauma and psychiatry.

While this book might be regarded by the electroencephalographer as an elementary text-book, to the practising psychiatrist and neurologist it is an indispensable work.

We have often stressed the fact, too often overlooked, that our work as psychiatrists is based on a wide knowledge not only of medicine, but of the fundamental subject of physiology. This book, therefore, is one to be faced and read by all psychiatrists ; they will be wiser men, although no doubt sadder at finding that their training may not have fitted them to understand much that is written in this fine production.

G. W. T. H. FLEMING.

Freud : Dictionary of Psychoanalysis. Edited by NANDOR FODOR and FRANK GAYNOR. New York : Philosophical Library, 1950. Pp. 208. \$3.75.

This valuable little book is not a dictionary in the usual sense of the term. If one just wishes to know the meaning of a word used in psychoanalysis one can be served much better by other available dictionaries. This book, on the contrary, is a collection, arranged alphabetically, of excerpts with references, from the writings of Freud. Nowhere in the book is the work of any other psychoanalyst mentioned. The first word of the title is therefore accurate.

Under the heading Agoraphobia is a quotation more than half a page in length, in which Freud gave his view of the psychopathology of agoraphobia, and took for granted that the reader knew the meaning of the word. This kind of omission, however, is of no importance in this "dictionary" if the reader, knowing the meaning of the word, still wishes to know what Freud said about it.

There are some surprising omissions ; for example, there are no quotations given for Censor, Abreaction or Introjection ; but this could be remedied in subsequent editions.

C. E. H. TURNER.

The Maggid of Caro. By HIRSCH LOEB GORDON, M.D. New York : Pardes Publishing House, Inc., The Shoulson Press, 1949. Pp. 396. Illus. 182.

Caro was a chief rabbi who lived from 1488-1575 ; and his Maggid was his familiar spirit. This Maggid would speak aloud out of Caro's mouth when he, Caro, was alone in his study.

Caro was an exceptionally able and studious person, who fulfilled his routine judicial functions for his people, wrote authoritative works, taught in his own academy and led a family life, but he was also at the same time a mystic and ascetic, who spent long hours by himself, and ate and drank frugally.

His Maggid gave him long and detailed instructions concerning every aspect of his life. The Maggid also told him how well he was thought of in the Celestial Academy and that worlds paid homage to him as a king of heavenly hosts.

In the sixteenth century there were several other maggids appearing to other mystics, and all of Caro's beliefs had precedents in the religious life and writings of the Jews.

The interest of the book, therefore, centres around the question of whether Caro was mentally ill or normal.

Caro's life, his religious background, the times and places in which he lived are all described by Dr. Gordon in detail. Verbatim accounts are given of the Maggid's instructions to Caro, who wrote them down in his secret diary. The book ends with an appraisal of the psychological possibilities to be considered in the diagnosis of the mental state of this illustrious man, the most outstanding scholar of his generation.

Dr. Gordon was brought up in a Caro-dominated atmosphere, for his father was a rabbi who studied and recited the works of Caro incessantly ; and writing of his father, Dr. Gordon says, " In my ears still rings his soft melodious voice reciting Caro's wisdom." Steeped therefore in his subject the author of *The Maggid of Caro* gives a brilliant survey of the facts, but he comes to no conclusion. It would have been more courageous if Dr. Gordon had developed his unspoken but underlying theme of the value of religious delusions. That would have made an even finer contribution to his subject.

C. E. H. TURNER.

Part III.—Bibliography and Epitome.*

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* A number of extracts in this section are reproduced from *Chemical Abstracts* and *Psychological Abstracts*. To the Editors of these two Journals we extend our grateful thanks.

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Remarks on Electroencephalography in Cerebral Abscess.

Seven cases diagnosed as cerebral abscess have been examined by E.E.G. In 3 of them pus-filled cavities were found by operation, in 1 by post mortem examination (Group I). Three patients (Group II) were treated with chemotherapy alone.

But for the patient who died shortly after admission to the hospital, all the patients were examined repeatedly during the convalescent period. In all patients focal dysrhythmias were found.

The material is too small for definite conclusions to be drawn, but the author feels assured that the following statements are warranted:

(a) E.E.G. is of great value for a localization of cerebral abscess, partly because the dysrhythmia occurs at an early stage of the illness.

(b) Repeated E.E.G.'s in the convalescent period are of importance for an evaluation of the treatment, and may give hints about prognosis as to late complications.

(c) In some cases of recent abscess or incipient abscess it may possibly be an indication to try treatment with chemotherapy alone, provided repeated E.E.G.'s at frequent intervals can be carried out.

(d) The dysrhythmia in recent abscess seems to be so severe that E.E.G. may give some information not only about the localization, but also about the nature of the focus recorded. E.E.G. in cases of recent abscess seems to give more severe dysrhythmias than in cases with a comparatively long history of illness, the rapidity of the expanding process here being a deciding factor.

(e) The combination E.E.G.-cerebral angiography, in addition to the clinical examination, is very useful for the exact localization of cerebral abscess.

(Author's abstr.)

A Study of the Potassium and Sodium Content of the Blood Serum in Schizophrenic Subjects.

First the writer gives an account of the hormonal function of the adrenal glands, especially the mode of action of the cortical hormone. Then follows a review of part of the literature available on the biological aspects of schizophrenia, particularly that dealing with adrenal dysfunction. The technique used in determining serum sodium and serum potassium is described, and an account is given of the accuracy of the analysis and the calculations in determining the mean error on each individual analysis and the mean error on the mean value.

The normal material is presented. The results of the analyses show that serum sodium ranges from 329.2 to 353.0 mgm. per cent., mean value 337.9 mgm. per cent. ± 1.55 . Serum potassium ranges from 16.8 to 21.0 mgm. per cent., mean value 18.8 mgm. per cent. ± 0.30 . All the results accord well with the findings of earlier workers.

After reporting the case-histories the writer proceeds to give the results of the analyses among the schizophrenic patients who were divided into 2 groups. Group I including recent cases, i.e. psychoses of up to 2 years' standing, and Group II, psychoses of longer duration. In Group I the serum sodium ranges from 330.0 to 342.3 mgm. per cent., mean value 335.0 mgm. per cent. = 1.2, whereas serum potassium ranges from 16.9 to 22.6 mgm. per cent., mean value 19.7 mgm. per cent. = 0.55. In Group II serum sodium ranges from 327.6 to 339.9 mgm. per cent., mean value 332.3 mgm. per cent. = 1.0, whereas serum potassium ranges from 17.2 to 21.5 mgm. per cent., mean value 18.6 = 0.34.

Discussing the results, the writer arrives at the conclusion that, as far as serum sodium is concerned, all the individual values are within normal limits, whereas the mean value representing the acute, and particularly the chronic, cases is lower than the mean value found in normal subjects. Serum potassium does not appear to show any definite abnormality. The mean value representing the acute cases is rather high compared with the mean value in the normal material, but not high enough to be pathological.

The results are interpreted as a further support of the theory that the adrenal glands are a link in the pathogenesis of schizophrenia without, however, being an active factor in starting the process.

(Author's abstr.)

Determinations of Glutamine and Glutamic Acid in a Material of Mental Patients.

Determinations of glutamic acid and glutamine in the plasma of 150 patients with mental affections have shown decreased glutamic acid values in various psychotic states, especially in schizophrenia in the active phases, and in convulsive patients in a few cases.

Besides, increased glutamine values have been demonstrated in schizophrenics in the active phase, and in convulsive patients. (Author's abstr.)

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Nonconvulsive Electric Stimulation Therapy: Its Place in the Treatment of Affective Disorders, with Notes on the Reciprocal Relationship of Anxiety and Depression.

Convulsive treatment through frontal leads inhibits respiration temporarily; non-convulsive treatment through frontal or temporoparietal leads stimulates respiration.

Convulsive treatment through frontal leads relieves depression but reduces awareness for memory content and may enhance anxiety, while nonconvulsive treatment through temporoparietal leads relieves anxiety and restores awareness for memory content, but may enhance depression. By using both, it is possible to avoid the "untreatable" residua after electroshock treatment.

(Author's abstr.)

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Comparative Results in Seizure Control Using Phenobarbital, Dilantin, and Mesantoin.

The advent of each new drug that proves effective in hitherto uncontrolled cases of *grand mal* epilepsy is heralded by the press and others as the wonder drug that promises more than any other drug we have had available in the past. The toxic reactions, though reported, are often glossed over as if they were not of serious consideration. If the temporal order of introduction of the 3 discussed drugs were reversed, we can well imagine the resultant enthusiasm of workers and the press. Phenobarbital would surely be heralded as the drug of drugs that is practically non-toxic and that, at the same time, controls the seizures of as many patients as the other two drugs. Dilantin and Mesantoin each has a useful function in the control of convulsions, but only as a supplement and occasionally as a substitute in the unusual case not responsive to phenobarbital medication. It behoves us all to continue unremittingly our search for better methods of aiding

this type of patient, but our expressed enthusiasm in reporting our results should be tempered by the knowledge that to date we have not presented a single drug for *grand mal* epilepsy that can be considered more than a supplement, and occasionally a substitute, for phenobarbital, which has remained the drug of choice since its advent in 1912.

(Author's abstr.)

Constitutional Factors in the Prognosis of Schizophrenia.

1. In a series of 2,100 consecutive admissions to the Veterans' Administration Hospital, Lyons, N.J., 72 per cent. of the schizophrenics were photographed in the standardized somatotype position shortly after admission.

2. These somatotype photographs were rated by Dr. William H. Sheldon, who had no knowledge as to the diagnosis, disposition, or any other pertinent information about the patients. Since these patients were included in a much larger series made up of psychoneurotics, neurological cases, and non-neuropsychiatric patients, in addition to the schizophrenics, the rater had no way of knowing even that they were schizophrenics.

3. The patients were allowed to follow their normal course in the hospital without awareness on the part of the staff as to their somatotype rating. The staff had no particular training in possible relationships between somatotype and psychiatric factors.

4. In all, 1,000 relatively consecutive admissions were somatotyped in the present series, and an extremely detailed review made of all pertinent material, including records while in service, laboratory data, cardiac and E.E.G. consultations, symptomatology, etc.

5. Two years after the first patient in the series was admitted (and 6 months after the last series admission), the disposition of the patients was reviewed.

6. There was found to be a significantly positive correlation between mesomorphy and good prognosis and a suggestively poor one with high endomorphy.

7. This correlation between prognosis and somatotype proved to be independent of correlations between somatotype and diagnosis. In other words, relationship between prognosis and somatotype is more basic than relationship between prognosis and diagnostic subcategory.

8. Significant correlations were found to exist between somatotype and diagnosis: mesomorphs tended to be paranoid and hebephrenic, whereas ectomorphs tended to be hebephrenic and not paranoid.

9. It was also found that those who were overendowed and underendowed from an absolute point of view, had a poor prognosis.

10. On the basis of other parts of the study, it is suggested that with the somatotype as a frame of reference a much-needed factor will be introduced into the organic approach to schizophrenia, making comprehensible much of the data that are now characterized only by their great variability. (Authors' abstr.)

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Effect of Treatment on Excretion of 17-Ketosteroids in Patients with Mental Disease.

The daily excretion of 17-ketosteroids is in or slightly above the normal range in patients with psychoses or severe neuroses. The values found are high if the reduced caloric intake of the patients is considered.

Early in the course of psychotherapy, insulin therapy or electric shock therapy, increased excretion of 17-ketosteroids may occur. Late in the course of treatment, and after it, a diminution in output is found in patients who show notable improvement, whereas no decrease occurs in patients who are not improved. These changes may be masked by an increase in excretion of 17-ketosteroids when an increase in caloric intake occurs in association with remission of the psychosis.

(Authors' abstr.)

The Cerebrospinal Fluid in Methyl Alcohol Poisoning.

Sixty-four spinal punctures were performed on 13 patients with acute methyl alcohol poisoning. Abnormal elevation of spinal fluid pressure occurred in 5 of 11 patients throughout a five-week period of convalescence.

In 8 of 10 patients spinal puncture performed on the third day after ingestion of the poison showed elevated pressures. Two had pressures of 300 and 390 mm. of water, respectively; 3, a pressure of over 200 mm. of water, and 3, pressures of over 150 mm. of water.

All patients known or suspected of having ingested methyl alcohol should have repeated determinations of the spinal fluid pressure during the week following ingestion, in addition to the accepted standard procedures. Elevated pressures should be reduced by drainage. By this procedure, toxic metabolic products may be removed.

It is not possible to determine from clinical findings in the conscious patient the presence of an increased cerebrospinal fluid pressure. Direct manometric measurement is therefore indicated to determine the spinal fluid pressure in all suspected cases. This procedure was judged to be an important emergency and therapeutic measure.

Death apparently occurs as a result of accumulative toxic products. The effects of abnormal cerebrospinal fluid pressure on the central nervous system are reflected in delirium, coma, convulsions and central respiratory depression, in the presence of acidosis.

Generally, patients with the most obvious ophthalmoscopic changes also had abnormally high spinal fluid pressures.

(Author's abstr.)

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Effects of A.C.T.H. in Patients with Mental Disease.

It seems clear that in patients with schizophrenia or depression of any duration the reaction of the adrenal cortex to certain physical stresses and to the injection of A.C.T.H. is not diminished as compared with the changes observed in non-psychotic subjects. It is possible, moreover, that psychotic patients show exaggerated metabolic changes after the injection of A.C.T.H. If the latter observation should prove valid, it might be possible to relate psychosis to metabolic

changes consequent to an unusual response of the adrenal cortex to A.C.T.H. or of the tissue to cortical hormone released during ordinary stresses.

Changes in eosinophil count, uric acid and 17-ketosteroid excretion and sweat sodium concentration after the injection of A.C.T.H. are not diminished in psychotic patients as compared with the changes in non-psychotic subjects. Patients with schizophrenia or manic-depressive psychoses appear to show greater than normal changes in carbohydrate metabolism after the injection of A.C.T.H.

(Authors' abstr.)

Colloidal Gold Reaction in Multiple Sclerosis.

The quantitative colloidal gold test as performed at, and reported by, the Division of Laboratories and Research of the New York State Department of Health is a valuable aid in the diagnosis of multiple sclerosis.

Multiple sclerosis was the presumptive diagnosis in 64 per cent. of the 263 cases of non-syphilitic disorders in which the spinal fluid showed a type D colloidal gold reaction of one or another strength. Some form of the type D reaction was also found in 36 per cent. of a miscellaneous series of disorders of the central nervous system. These findings are in accord with the known lack of specificity of the type D reactions for this or any other disease.

On the other hand, the type D reactions were present in 94 per cent. of 158 cases with a "definite diagnosis" of multiple sclerosis, and in 83 per cent. of 203 cases in which this disorder was either definitely diagnosed or reasonably suspected. Therefore, the absence of the type D reaction (i.e. the presence of any other type of curve) renders a diagnosis of multiple sclerosis uncertain.

The strong type D reaction (exclusive of weak and minimal types) was found less commonly (46 per cent.), but was more indicative of the disease, as it occurred rarely (8 per cent.) in non-syphilitic patients without multiple sclerosis.

The presence of the type D colloidal gold reaction in cases of multiple sclerosis and syphilis of the central nervous system closely parallels the relative increase in gamma globulins over albumin in the cerebrospinal fluid, as reported by the other observers.

The total proteins were moderately increased in 36 per cent. of our cases of multiple sclerosis.

The cerebrospinal fluid cell count was increased to above 10 cells per cubic millimeter in only 8 per cent. of the cases of multiple sclerosis.

No correlation was found between the duration, stage or clinical activity of the disorder and the colloidal gold reaction, total protein concentration or cell count of the cerebrospinal fluid.

(Authors' abstr.)

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Cortical Rhythms Not Seen in the Electroencephalogram.

(1) Two examples are described of records made from electrodes inserted in the brain across the cortex which have been compared with the E.E.G. Normal rhythms, abnormal rhythms and random wave complexes, all of high voltage, arose in the cortex, but could not be recorded from the overlaying scalp using accepted electroencephalographic techniques.

(2) In some cases the electroencephalogram does not reflect the electrical potential changes arising in the underlying cortex. This fact can be related to the individual variations and anomalies which have been observed in the E.E.G.'s of some normal and abnormal subjects, and it requires further study.

(3) A possible explanation of the absence of potential changes at the scalp when marked rhythmic changes can be recorded through the underlying cortex is that the potential changes are occurring through the depth of the cortex from many points, but reach its surface synchronously. (Authors' abst.)

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An Experimental Study of the Mechanism of Photic Activation in Idiopathic Epilepsy.

A single photic stimulus to the eyes of a normal animal gives rise, after a latency of 15 to 20 m.sec., to a response in the lateral geniculate body and in the primary and secondary visual cortices. This discharge may comprise one or three of the following components: (1) A rapid triphasic wave (initially positive, then negative, and finally positive); (2) a repetitive wave of alpha frequency; (3) a very slow wave of delta frequency.

Intermittent rhythmic photic stimulation produces a simplification of the cortical responses by a progressive cutting off of its slowest components and by a tendency to bring about a telescoping of the different components.

The local application of strychnine augments the amplitude and the duration of the negative second phase of component 1 and suppresses components (2) and (3).

The intravenous injection of Metrazol brings about an augmentation of the three components of the response, particularly component (3), even if attenuation has occurred as the result of a previous local application of strychnine. Intermittent photic stimulation at an approximate frequency of 3 c./sec. brings about, under these conditions, a repetition of the above responses. By two methods of simplification ("amputation" and "telescoping") the response assumes the typical form of the spontaneous discharge of idiopathic epilepsy—the spike and wave complex. It has been pointed out that this may be wrongly interpreted as being composed only of a negative spike followed by a slow wave of similar sign.

Under these same conditions of intravenous Metrazol injection, the topography of the response changes markedly when a certain concentration is attained. Suddenly it irradiates to the thalamic nuclei and to other regions of the cortex, where it predominates in or may even be localized to fronto-precentral regions. The latency of this irradiated response is of the order of 25 m.sec. in the thalamus and 30 m.sec. on the cortex. Each of these responses is accompanied by a muscular twitch of the extremities predominant in flexion. This latter is not suppressed by the complete ablation or freezing of the precentral sensorimotor cortex.

The injection of Tridione electively brings about the disappearance of the irradiated response without producing an alteration in the primary visual response. Phenobarbital in high concentrations causes the disappearance of the irradiated as well as the primary responses.

The ablation, isolation and freezing of the visual cortex or of any other cortical area on one side only does not suppress the irradiation response nor the bilateral myoclonic jerk, which accompanies it. The isolation of the visual cortex on both sides by section of its cortico-cortical connections is equally ineffective. Bilateral ablation, however, brings about the disappearance of the irradiated response and myoclonic jerk. From these findings the authors have concluded that the irradiated response is elaborated in the thalamus. It appears to result from an abnormal permeability of the thalamic synapses to the convergent action of impulses derived from the visual pathways. These latter include an essential relay in the visual cortex. The authors' believe that idiopathic epilepsy with its bilaterally synchronous negative spike and wave involves similar mechanism.

(Authors' abstr.)

The Electroencephalogram During Hyperventilation followed by Apnoea (A Preliminary Report).

(1) Following hyperventilation, the period of involuntary apnoea was reinforced by voluntary breath-holding. After an interval of normal record, high voltage slow waves similar to those during hyperventilation returned. This

response was observed to a variable degree in 36 of 50 subjects, and was accompanied by cyanosis.

(2) In two subjects with idiopathic epilepsy, apnoea activated typical E.E.G. spike and wave discharges.

(3) An attempt is made to interpret these findings in the light of the two main theories as to the mechanism by which hyperventilation affects the brain and activates the E.E.G. (the hypocapnia and the hypoxia or ischemia theories). The evidence, although indirect, appears to support the hypoxia theory.

(Author's abstr.)

Studies of the Regulatory Functions of the Anterior Limbic Cortex.

1. Stimulation of the anterior limbic area, and infra-limbic area, can produce three general types of changes in electrical activity. These responses have in common : That they can occur in all areas of cortex bilaterally at the same time ; that they occur immediately when elicited by electrical stimulation ; and that they act via cortico-subcortical mechanisms.

The types of changes in electrical activity affected are :

(a) *Attenuation.*

(1) Decrease in voltage without change in pattern.

(2) Decrease in voltage with decreased number of bursts or with simplification of burst patterns.

(b) *Augmentation* of bursts.

(c) *Activation* or "arousal" responses.

(1) With decreased voltage.

(2) With increased voltage.

Subcortical mechanisms by which these effects may be produced have been suggested.

2. The anterior limbic cortex ("24's") cannot be accurately described as a "suppressor area" on the basis of its electrical properties. This is based upon two facts :

(1) That type of electrical response called "suppression" in the literature, and attributed to this area as a localizable property has been shown to be the phenomenon of spreading depression which has no such local characteristics.

(2) Attenuation of cortical electrical activity (which differs markedly from the "suppressor" response described in the literature) can be evoked by stimulation of this area ; but so also can the contrasting types of responses in electrical activity herein called augmentation and activation.

The term "regulatory" seems to describe the functional properties of anterior limbic cortex better than "suppressor."

3. It has been suggested that intimate relationships exist between phylogenetically old areas of the brain, i.e. the "mesocortex" of the anterior limbic regions, the thalamic reticular system, and the reticular formations in hypothalamus, sub-thalamus and brain stem ; all possessing important regulatory control of cortical electrical activity and function.

(Authors' abstr.)

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Preliminary Report on Sixty-two Prefrontal Lobotomies on Psychotic Male Veterans at the Veteran's Hospital, Northport, Long Island, New York.

1. Results of prefrontal lobotomy in 62 patients during a three and one-half year period reveal that 37 per cent. are markedly, 29 per cent. are moderately, 27 per cent. are slightly improved, 7 per cent. are unimproved. None are in remission and none are worse.

2. Loss of agitated, self-destructive and disturbed behavior in chronic psychotic patients is the outstanding accomplishment of lobotomy in a substantial percentage of the cases selected.

3. In this series, catatonics and hebephrenics showed greater improvement than other types of schizophrenia.

4. Twelve of the patients had convulsions following lobotomy, 6 of whom had no previous shock therapy. Average time between operation and onset of convulsions was six and one-half months.

5. Patients under 40 years of age showed a slight tendency to better response after lobotomy than older patients.

6. Normal E.E.G.s post-operatively reflect a greater degree of improvement in patients than do abnormal ones.

7. In this series the E.E.G. was not found to be a valuable guide to indicate which patients would develop post-operative convulsions. (Author's abstr.)

NOVEMBER.

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- *A Report on the Current Status of an Attempt to Correlate Abnormality of Distribution of One Brain Enzyme with Mental Dysfunction. *Ashby, W.* . . . 425

Experiences with Antabuse Treatment of Alcoholism in a General Hospital.

In 35 consecutive private hospital admissions for alcoholism, antabuse was contraindicated in 8 and administered in 27. In 16 patients, followed three to nine months, there was full co-operation with treatment and no return to alcohol. In 4 cases there was at least one episode of drinking, but the patients continued to co-operate with treatment and attained partial success. In 7 cases, including 3 in which antabuse was stopped because of organic disease, treatment was unsuccessful. Insufficient insight and lack of family co-operation account for 4 failures.

The importance of detecting cardiovascular and hepatic disease as contraindications, the potential dangers of the test with alcohol and the necessity of continuous supervision by nurse and physician throughout the test reaction have been stressed. Sustained results depend upon individual psychotherapy, family co-operation, careful follow-up and control of side reactions of the drug.

(1) Treatment should be instituted only within a hospital because of hazards involved.

(2) Further evaluation is necessary before the final status of antabuse in the physiologic control of alcoholism can be established.

(3) Patients with evidence of pre-existing liver or brain disease should be closely observed for the development of abnormal mental symptoms.

(4) There is need for further research, particularly in hope of finding safer and less toxic drugs.

(5) Antabuse should not be released for general use until these problems have been settled.

(6) Despite these limitations, with careful selection of patients, personal management under hospital conditions, close follow-up and adjuvant therapy, treatment with antabuse shows great promise.

(7) We believe that the principle of a physiologic antagonist to alcohol is basic in order to control the chronic compulsive type of drinker. Purely psychologic management is inadequate. (Authors' abstr.)

Thyroid Function in Mental Disease. A Multiple Test Survey.

(1) Thyroid function in groups of schizophrenic, manic and depressive patients is significantly different from normal controls as measured by a pattern of the four tests used in this study, but is normal by clinical evaluation, and the test results fall within the normal range. The pattern for the psychoneurotic group is most like the normal.

(2) Thyroid function in schizophrenic, manic and depressive patients is significantly different from patients with thyrotoxicosis and myxedema, in that the test results fall within the normal range, and the patterns of test results on all four tests taken together are unlike those in patients with known thyroid disease.

(3) Thyroid function in schizophrenic, manic, depressive and psychoneurotic patients is different among the four groups. The patterns of test results are different with many seeming inconsistencies. (Authors' abstr.)

A Report on the Current Status of an Attempt to Correlate Abnormality of Distribution of One Brain Enzyme with Mental Dysfunction.

Data from a study of a single enzyme, carbonic anhydrase, have been presented which indicate a functional chemoarchitecture of the central nervous system.

Certain findings have been presented which suggest that disturbances in the contours of this quantitative distribution pattern may result in disturbed mental reactions.

The case incidence, with reference to the enzyme level found in the frontal pole, has been plotted from data on patients with parietic neurosyphilis, cerebral arteriosclerosis, dementia praecox, and on non-hospitalized persons.

The low level of the enzyme found in a considerable proportion of the cases of dementia praecox, and also found in cases where there is a known injurious agent, suggests an organic origin, either endogenous or exogenous, in at least some categories of this so-called functional disease. (Author's abstr.)

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*Electrocorticographic Effects of Stimulation of Posterior Orbital, Temporal and Cingulate Areas of <i>Macaca mulatta</i> . <i>Lennox, M. A., et al.</i>	383

Gastric Motor Effects of Acute Removal of Cingulate Gyrus and Section of Brain Stem.

1. Bilateral ablation of the cingulate gyrus in acute experiments in dogs under chloralose-urethane anesthesia produces a moderate increase in the rate of contraction of the pyloric antrum.
2. Intercolliculo-mesencephalic brain stem section increases the pyloric antral rate to a greater degree than cingulate ablation.
3. Hypothalamic ablation produces an increase in pyloric rate which is not further affected by brain stem section.
4. Evidence is presented that these effects are not due to traumatic stimulation. (Authors' abstr.)

Some Physical and Pharmacological Factors Affecting Delayed Response Performance of Baboons following Frontal Lobotomy.

1. Two immature female Chacma baboons (*Papio porcarius*) were trained in the delayed response situation, subjected to bilateral frontal lobotomy, and retested under various physical and pharmacological conditions.
2. The animals showed a low level of performance in the delayed response situation for six months postoperatively under normal conditions (food intake approximately 350 calories per day, temperature approximately 80°).
3. The following conditions significantly improved test performance: Intramuscular injection of Nembutal in approximately half the anesthetic dose; the intramuscular injection of 0.25-0.50 unit of insulin per kgm. body weight; a reduction of the environmental temperature by 15°-20° for three hours before testing; fasting for 48-60 hours before testing.
4. Benzadrine (5 mgm.), elevation of the environmental temperature for three hours before testing, and prefeeding immediately before testing, resulted in a few chance trials or complete refusal to test.
5. The relationship of these physical and pharmacological changes to energy metabolism is discussed; those alterations in conditions which temporarily increase food intake increase test scores; those which temporarily decrease food intake impair performance.

6. The nature of the impairment in delayed response performance following frontal lesions is discussed.

7. The physical changes and pharmacological agents used have been shown to affect central neural mechanisms. The significance of the relation between these mechanisms and frontal lesions and their behavioral implications are pointed out. (Author's abstr.)

Electrocorticographic Effects of Stimulation of Posterior Orbital, Temporal and Cingulate Areas of Macaca mulatta.

1. Unelicited spikes were recorded frequently from the periamygdaloid cortex, temporal pole, and posterior orbital areas, and simultaneously at needle electrodes in the region of the amygdala and hippocampus.

2. Electrical stimulation of the periamygdaloid temporal polar, posterior orbital and anterior cingulate areas produced similar electrocorticographic effects: (i) Elimination of strychnine spikes in areas other than that stimulated; (ii) elimination of unelicited spikes in areas other than that stimulated; (iii) production of an after-discharge locally and sometimes in areas other than that stimulated.

3. These effects were independent of one another, in that each might occur alone or in any combination with others.

4. Certain areal differences were noted. Stimulation of the anterior supracallosal area and of the temporal pole produced all effects. Stimulation of the periamygdaloid cortex produced a seizure discharge in all trials. Stimulation of the posterior orbital area eliminated strychnine and spontaneous spikes but did not result in a seizure discharge. No effect was produced by stimulation of the pre- or subcallosal areas.

5. Some implications of these findings with respect to the mechanisms involved in psychomotor epilepsies are discussed. (Authors' abstr.)

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*Spike Discharges of Single Units in the Cerebellar Cortex. <i>Brookhart, J. M., et al.</i>	465

The Elementary Vestibulo-ocular Reflex Arc.

Artificial endolymph currents have been produced in different semicircular ducts of cats and dogs through fine glass cannulas introduced under the control of a stereoscopic microscope into the ducts with the aid of a micromanipulator. In some cases the posterior semicircular duct was stimulated in a similar way after extirpation of the utriculus, sacculus and the membranous ampullae of the superior and lateral semicircular duct. The activity of the extra-ocular muscles has been recorded simultaneously on a kymograph.

The receptors of the vertical semicircular duct are—as was described first by Ewald and recently by many other authors—more responsive to endolymph currents of the direction “from the ampulla,” the receptors of the horizontal ducts to those “toward the ampulla.”

From stimulation of the different semicircular ducts it appears that there is a predominant functional correlation between any crista and two of the extra-ocular muscles. The crista of the superior semicircular duct has a predominant connection with the ipsilateral superior rectus and the contralateral inferior obliquus; the crista of the posterior duct with the ipsilateral superior obliquus and the contralateral inferior rectus; the crista of the horizontal duct with the ipsilateral and medial rectus and the contralateral lateral rectus.

This functional correlation is in accordance with previous anatomical investigations concerning the pattern of the three-neuron-reflex-arc between labyrinth and extra-ocular muscles. From this agreement it may be inferred that the predominant correlation between any crista and two extra-ocular muscles is established by the elementary vestibulo-ocular reflex arc, in which three neurons are involved. This assumption is supported by the results of experiments with transection of the posterior longitudinal fasciculus, and of the pons with the exception of the former tract.

Besides the elementary three-neuron-arc there exists—as was first clearly shown by Lorente de Nó—numerous arcs, most of them closed through the reticular formation, by way of which the impulses from any labyrinthine receptor may be brought into connection with any one of the extra-ocular muscles. The function of the reticular formation seems to be essential, especially for elaboration of inhibitory responses. Nystagmus is generally suppressed by this mode of stimulation, for which fact no adequate explanation can be given, but it was advantageous for investigation of the function of the elementary arc, which thus became more dominant.
(Authors' abstr.)

Trigeminal Neurotomy and Blood Pressure Responses from Stimulus of Lateral Cerebral Cortex of Macaca mulatta.

These results were obtained under the conditions usually present in acute experimental studies involving the cerebral cortex. Since stimulation of so many cortical points resulted in marked changes of blood pressure, such changes must be taken into consideration in evaluating the results of the effects of cortical stimulation on all physiological systems.

The most likely explanation of the effect of trigeminal section on the responsiveness of the cortex is that afferents from the cortical vessels have been interrupted. However, since, in unanesthetized humans no pain is elicited from stimulation of blood vessels on the lateral surface except near sinuses, it is somewhat surprising to find so widespread a distribution of afferents in the monkey. It is, therefore, possible that an intact trigeminal nerve potentiates cortical responses to stimulation either by an effect on cerebral circulation or a direct neural synergism. However, the effect of trigeminal section is mediated, these results suggest that a separate autonomic mechanism involving the trigeminal nerve exists on the surface of the cortex.
(Authors' abstr.)

Field of Retinal Induction and Optical Illusion.

1. The field of retinal induction around a retinal image was mapped out by employing the method used previously in physiological studies on simultaneous color contrast, and it was found that the field was circular around a circle, triangular around a triangle, but cruciform around a square.

2. The induction at a point in the middle of the dark cross bounded by four yellow squares was found lower than at any other parts of the cross. The phenomenon was not so conspicuous on the oblique cross bounded by four rhombs. These physiological findings were in good agreement with our psychological experience.

3. Wertheimer-Benary's contrast, which is one of the most important psychological phenomena for Gestaltpsychology, was demonstrated more directly by our physiological method than by the psychological.

4. It was shown that the patterns of the field of retinal induction were closely connected with optical illusions of varying types—for example, the optical illusions of Müller-Lyer, of Zöllner, of Hering, of Köhler, etc. It seems likely that optical illusion takes place when the field around the retinal image of a figure is deformed by some modification of the figure or by the presence of the images of other figures.

5. The distance over which the field around a bar extended in the direction perpendicular to it was found longer in the vertical position of the bar than in the horizontal. So-called anisotropy of visual space seems to be based on such functional anisotropy of the retina.

6. The importance of retinal induction for visual acuity was emphasized, and the vernier effect with respect to visual acuity was accounted for on the basis of field patterns.

7. Qualitative differences of the field of retinal induction from the magnetic, electric and gravitational fields were shown by several examples, among which the

dependence of retinal induction upon the angle subtended by the inducing figure is the most fundamental. The mechanisms of contrast phenomena and optical illusions stated above were discussed on the basis of these peculiarities.

(Author's abstr.)

Biochemical and Physiological Differentiation during Morphogenesis. X. Onset of Electrical Activity in Developing Cerebral Cortex of Fetal Guinea-pig.

Rhythmic potentials can first be recorded from the cortex of the fetal guinea-pig at the 46th day of gestation (term 66 days), immediately following the period found to be critical for morphological and biochemical changes which are believed to accompany the differentiation of neuroblasts into neurones. Prompt production of strychnine spikes following local application of strychnine to the cortex provides evidence that the potentials are at least partly cortical in origin. The onset of cortical electrical activity is correlated temporally with evidence that can be interpreted to mean that the neurones of the cortex become permeable to sodium at this time.

(Authors' abstr.)

Termination of Spinal Afferents to Inferior Olive in Cat.

Lesions have been made at various levels of the spinal cord in 20 cats. The lesions involved different funiculi and/or the dorsal horns. The ensuing degeneration of terminal fibers and boutons in the inferior olive has been studied in silver preparations. The principal findings are the following:

1. The spinal fibers to the inferior olive ascend in the ventral funiculus, and some also in the adjoining part of the lateral funiculus. They appear to originate from all levels of the cord.

2. Somewhat more than half the number of fibers cross in the medulla spinalis.

3. The fibers terminate by means of typical terminal boutons on the perikarya and processes of the cells in certain parts of the inferior olive. Most, if not all, terminal fibers are collaterals from ascending fibers.

4. The bulk of the spino-olivary fibers reach the ventro-lateral part of the dorsal accessory olive and the ventro-lateral part of the caudal half of the medial accessory olive. Some fibers pass to two distinct small parts of the olive: the nucleus β and the dorso-medial cell column, and quite a few to the dorsal cap.

5. A comparison with the pattern of the olivo-cerebellar projection, studied previously reveals that spinal impulses are distributed by means of the olive in great numbers to the vermis of the anterior lobe, some to the pyramis, a few to the uvula and the decline and still fewer to the nucleus fastigii.

6. The fibers from the cervical and upper thoracic cord are far more scanty than those from the lumbo-sacral cord. There is some indication that the number of cervical and upper thoracic cord fibers reaching the olivary areas projecting on the lobulus centralis are even more scanty than those passing to the olivary areas sending their fibers to the culmen. It is suggested that the spino-cerebellar pathway through the external cuneate nucleus (considered commonly to be the cervical cord equivalent of Clarke's column) may represent an accessory pathway also for the spino-olivo-cerebellar system from higher levels of the cord.

7. The spino-olivo-cerebellar pathway with regard to its organization presents a striking similarity to the dorsal spino-cerebellar tract. The only difference appears to be that the impulses transmitted through the olive reach the vermis of the anterior lobe only, while the fibers of the dorsal spino-cerebellar tract terminate also in the intermediate parts of the anterior lobe. Together with other differences in fiber connections this emphasizes the importance of considering the subdivision of the anterior lobe in three longitudinal zones.

8. The anatomical findings tend to show that the "spinal" areas of the inferior olive function purely as relay stations. Impulses mediated through the spino-olivo-cerebellar pathway will reach the cerebellum later than those passing in the dorsal spino-cerebellar tract. The similarity in the organization of these two systems indicate a similarity in function. For anatomical reasons the spino-olivo-cerebellar system cannot be supposed to mediate tactile impulses to the cerebellum. The findings made in this study emphasize the necessity of considering the functional subdivision of the inferior olive in physiological experiments. Some of the reports on the physiology of the inferior are discussed.

(Authors' abstr.)

Some Functional Connections between Hypothalamus and Medulla.

Preliminary stimulus mapping of the posterior hypothalamus shows a pattern response similar to that described earlier for vasomotor responses, but in addition respiration and somatic reflexes were found generally to vary in the same direction as the blood pressure responses.

Interruption of the medial inhibitory reticular formation in the medulla served to enhance hypothalamic facilitation of vasomotor, respiratory and somatic reflexes.

Interruption of the dorsolateral facilitatory reticular formation resulted in a depression or abolition of hypothalamically induced facilitation of vasomotor, cardiac, respiratory and somatic reflexes.

Simultaneous stimulation of the bulbar inhibitory system opposed hypothalamically induced vasopressor responses to the same extent that uncomplicated stimulation of this system caused vasodepression.

Further evidence is presented to indicate that the bulbar facilitatory and inhibitory systems, activated by the posterior hypothalamus, influence vasomotor, respiratory and somatic activity in the same direction. (Authors' abstr.)

Spike Discharges of Single Units in the Cerebellar Cortex.

Spike potentials of single units have been recorded from the cerebellar cortex of decerebrated or anesthetized cats through the use of fine, wire microelectrodes which circumvent the detrimental influences of cerebellar movement and pressure which make the use of rigid electrodes unsatisfactory.

Intrinsic cerebellar neurons were found to be spontaneously active at frequencies ranging from 20 to 125 per sec., with the majority falling in the range of 70-80 per sec. This activity occurred in erratic bursts of variable length separated by silent intervals of variable duration. Factors controlling the resting frequency and the timing of the periods of activity and silence have not been determined.

The identity of the unit producing this activity is unknown. Activity in intrinsic units may be differentiated from activity in extrinsic, or afferent, units through the use of local strychnine and through differences in the responses of the two types of units to sensory stimulation. The intrinsic units were active in animals with chronic surgical isolation of areas of the cerebellar cortex.

Local strychnine applied to the cerebellar cortex produces characteristic convulsive, avalanching outbursts of activity in intrinsic cerebellar neurons. Similar patterns of activity are also produced by other forms of intense stimulation.

Some responses of cerebellar neurons to afferent volleys over spinocerebellar paths and over cortico-ponto-cerebellar paths are described. It has been possible to evoke, to augment and to inhibit activity in cerebellar neurons by such afferent stimulation. (Authors' abstr.)

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A Rorschach Study of a Group of Medical Students.

1. The individual Rorschach scores of 60 fourth-year medical students were statistically analyzed and compared with those of various groups of superior adults reported by other investigators.

2. In the intellectual sphere the 60 medical students were similar to other superior adults in productivity, intellectual drive and organizational energy, form accuracy and originality of interest content; they differed from other superior adults in the emphasis upon Dd (rare detail) in the mode of approach.

3. In the affective sphere these medical students resembled other superior adults in richness of sources of energy available for adjustment. They were unusual in the frequency with which both shading and colour shock were noted.

4. The experience balance of the medical students showed half of the total group to be introversive, while a quarter were extratensive and a quarter were approximately ambiequal.

5. The mean number of white space responses given by the medical students was significantly higher than in other groups.

6. The significance of various Rorschach variables in the total personality structure of medical students is discussed. (Author's abstr.)

The Anxiety Syndrome in Alcoholism.

In the study of 67 alcoholics, and a review of 38 cases previously studied, it was noted that, even in the cases where drinking started in childhood, the nervous tension with symptomatology of the anxiety syndrome observed at and after puberty, appeared to serve as the basis for the persistent use of alcohol. Why more individuals do not drink to satisfy their anxiety which would seem to be greatest at puberty is a problem that needs further study. It is the opinion of Schilder that alcoholics experience definite feelings of sexual inferiority. Banay has suggested that alcohol may become a substitute for sex gratification and points to a psychosexual problem in alcoholics. Moore has noted that alcohol is used to relieve the nervous tension of drinkers, that this drinking usually started while young, that inadequate preparation for, or information about, sex was a factor for pertinent consideration. Karpman, too, has considered the alcoholic very definitely as a neurotic, while Kraines attributes addiction to a determined internal drive. The findings of these authors are parallel with many of the present observations. The studies by Stevenson into the causes given by patients for their drinking revealed, as did the present one, that they have no deep insight into their basic cause for drinking.

The return of alcoholics to the mother or mother-substitute following separation or divorce on the part of the male; or the return of the female to the father is one point which needs further study. The frequent findings of equal regard for wife and mother, with a leaning slightly toward the mother, is a pertinent observation.

Norberry has noted strong filial over-dependence in his cases, while parental training and attitude would seem pertinent to Schilder. In this respect, Knight has noted that most alcoholics have been married and divorced at least once, so that adjustment to marriage constituted a problem to them. Moore has described an attachment of males to their mothers greater than the average, noting some infantile and immature patterns of behaviour as well, all of which were observed in this study. All in all, it showed that marriage as a way of life was not fully accepted by the alcoholics studied.

Strecker has noted that the alcoholic is preponderantly an introvert. This, the author believes, is definitely associated with psychosexual behaviour and, hence creates part of the difficulty in making a satisfactory proper heterosexual adjustment.

The wish to escape reality, as noted by Peabody should be carefully evaluated, since the incidence has been noted as being originally psychosexual and later extending to all difficulties encountered. Moore has observed the need of alcohol to sublimate the emotions in the alcoholic.

While the cases studied were too few from which to draw definite conclusions, certain trends were noted.

(1) The symptoms that seemingly provoked alcoholism or caused its persistent use were those of the anxiety syndrome and occurred mostly at puberty. (2) Alcohol was found capable of relieving such symptoms, but gradually increasing amounts were necessary. (3) Whenever an emotional upset or problem arose thereafter alcohol was tried as the best means of relieving the unpleasant feeling or situation, and eventually the condition was blamed for alcoholism—hence the many reasons given for it. (4) Alcoholics seem to remain with their marital partners chiefly when the partner is "tremendously in love" with the non-drinking personality of the alcoholic. (5) Regardless of whether a satisfactory sexual adjustment is established at marriage, if the first method of meeting this problem was with alcohol, the patient will still at intervals, resort to long periods of heavy drinking. (Author's abstr.)

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1. Biochemistry, Physiology, Pathology, &c.

Activity of Cholinesterase in (Various) Organs and the Action of Adrenaline on this Activity. Speranskaya, E. N. [Doklady Akad. Nauk S.S.S.R., **71**, 411-13 (1950).]

The cholinesterase activity of a group of specimens (frog liver) is a variable quantity; in 100 specimens 48 per cent. had very high activity, 35 per cent. a medium value, and 17 per cent. a very low one. Lowering the functional activity of the organ (liver) also lowers the enzyme activity; in hypophysectomized frogs only 8 per cent. had high cholinesterase activity, 16 per cent. medium and 76 per cent. low. Action of adrenaline depends on initial cholinesterase level and on the dosage of adrenaline (1×10^{-7} to 1×10^{-10} concentration). The high activity of cholinesterase is usually depressed by the drug, but a low activity of tissue cholinesterase is raised by adrenaline; the effects are most pronounced at 10^{-8} - 10^{-9} concentration of the drug.

G. M. KOSOLAPOFF (Chem. Abstr.).

Electrophysiological Analysis of the Action of Acetylcholine on Nerve Centers. II. Action of Eserine, Prostigmine and Atropine on the Electrical Activity of the Visual Lobes of a Frog. Artem'ev, V. V., and Babskii, E. B. (Lenin State Pedagog. Inst., Moscow). [Fiziol. Zhur. (J. Physiol.), **36**, 151-60 (1950); cf. C. A., **44**, 4105b.]

Eserine or prostigmine at 1×10^{-5} to 2×10^{-5} concentration acting on the visual lobes of a frog enhance the spontaneous electric activity of the nerve centers. Atropine in similar concentration does not affect or lower the activity and completely eliminates (blocks) the action of acetylcholine; applied after the latter it leads to restoration of the normal oscillations, although reflex actions are not eliminated.

G. M. KOSOLAPOFF (Chem. Abstr.).

Relation Between the Reflex Erythemas following Intracutaneous Injection of Acetylcholine in Normal and Pathological Carbohydrate Metabolism. Kohler, V., Pennew, L., Heil, E., Vorbrugg, M., and Bauer, R. (Univ.-klinik, Wurzburg Ger.). [Endokrinologie, **27**, 35-45 (1950).]

The reflex erythema reaction in a normal subject is increased after injection of glucose. Likewise, after insulin injection, there is about 30 per cent. increase in the erythema reaction, during the hypoglycemia, whereas the erythema reaction decreases about 50 per cent. after adrenaline injection, while the blood-sugar level is raised. In patients with endogenous hypoglycemia, the erythema reaction is great, but as the blood-sugar level is raised the erythema reaction decreases. In precomatose diabetic patients with ketonuria the erythema reaction is relatively small, but increases during treatment.

S. MORGULIS (Chem. Abstr.).

Determination of the Proteins in the Spinal Fluid. Hinsberg, Karl, and Gleiss, Jörn. [Klein. Wochschr., **28**, 444-8 (1950).]

The protein content of 62 spinal fluids was determined by volumetric, photometric and chemical methods. The volumetric method (Kafka, C. A., **27**, 744) gave up to 40 per cent. lower values than those obtained with other methods. After establishing the optimum conditions for the formation of the biuret-protein color complex, the authors describe a photometric method, suitable for clinical use, which gave values practically identical with those obtained by determining the protein N by Kjeldahl procedure.

B. LUSTIG (Chem. Abstr.).

The Cerebrospinal Fluid in Premature Infants. Otila, Eino (Univ., Helsinki, Finland). [*Acta Paediat.*, **35**, Suppl. VIII, 100 pp. (1948) (in English)].

The yellow color of the cerebrospinal fluid (I) of newborn premature infants, obtained by lumbar puncture, is due chiefly to bilirubin. The cell count and amount of protein in (I) of the premature infant are considerably higher than those in normal (I) and moderately higher even than those in the (I) of the full-weight newborn infant. With premature infants of low birth weight the cell count and amount of protein in (I) are higher and maintain the elevated level for a longer period than those of premature infants with a higher birth weight. These elevated cell and protein values are believed to be due chiefly to the greatly increased meningeal permeability in premature infants, perhaps augmented in certain cases by a condition caused by cerebral hemorrhage *sub partu*. The results of tryptophan and mastic reactions suggest that the proteins present in (I) of the premature infant frequently differ somewhat in the first month of life and particularly in the neonatal period from the (I) proteins in later life. The (I) sugar values of the premature infant were fairly high and on an approximate level with the blood-sugar values determined simultaneously. This is attributed to the increased meningeal capacity in the premature infant. Following intramuscular administration uranin diffuses more rapidly and to a greater extent into the (I) of premature than of full-term, control infants.

RUTH BERGGREN (Chem. Abstr.).

Microphotometric Determination of Globulin and Total Protein in Cerebrospinal Fluid or Diluted Blood Serum. Salt, Harold B. (Roy. Infirmary, Worcester, Engl.). [*J. Lab. Clin. Med.*, **35**, 976-82 (1950).]

A photoelectric measuring device, equally suitable for absorptiometric or dispersimetric measurements is described. Total protein is detected in diluted blood serum or cerebrospinal fluid. The protein solution is added to salicysulfonic acid reagent and buffered gum ghatti reagent and the degree of light dispersion by the suspension is determined. Globulin is determined on diluted blood serum or on diluted cerebrospinal fluid. The protein solution in this case is added to gum ghatti reagent, NaCl solution, and MeOH and after incubation at 37° for 1 hour, the light dispersion value is determined. Standard reference graphs are prepared with known solutions of total protein and of globulin. Regular determinations are made with light of 700 mμ. wave length, but where concentrations are low it is advantageous to use light of 430 mμ. Protein in quantities of 0.1 to 1.4 mgm. per aliquot analyzed are determined.

W. DONALD GRAHAM (Chem. abstr.).

Vitamin B₁ in the Spinal Fluid in Inflammations of the Brain and the Meninges. Blume and Puschel (Dortmund, Ger.). [*Monatsschr. Kinderheilk.*, **98**, 147 (1950).]

Normal spinal fluid contains 1.2 to 1.9γ B₁ in 100 c.c. In hydrocephalus 0.9 to 1γ was found. Low values were found in tubercular meningitis and in one case of poliomyelitis. Intravenously administered vitamins B₁ appears promptly in the spinal fluid.

A. E. MEYER (Chem. Abstr.).

Changes in the Normal Spinal Fluid by the Action of Streptomycin. Araya, Norma Terra (Univ. Chile, Santiago). [*Farm. Chilena*, **24**, 201-3 (1950).]

Protein and Cl do not change, glucose increases rapidly.

A. E. MEYER (Chem. Abstr.).

Lead Content of Blood and Cerebrospinal Fluid in Experimental Lead Poisoning. Straube, Günther (Landesheilstätte, Hofheim, Ger.). [*Klin. Wochschr.*, **26**, 595-7 (1948).]

The presence of Pb could be detected in the blood of hamsters for the first time 4-5 days after the start of a daily oral Pb (OAc)₂ administration. The upper limit of blood Pb concentration before death occurred varied with different animals between 38-110γ per cent. The first Pb in the cerebrospinal fluid was detectable after the blood Pb concentration passed a 20γ per cent. level. Maximum Pb content encountered in cerebrospinal fluid amounted to 22γ per cent. The Pb blood and Pb cerebrospinal fluid contents rose and fell with each other, but the

latter always remained well below the level of the former. No Pb could be detected in the brains of animals which succumbed to Pb poisoning. The liver Pb concentration rose to about 60% per cent., and that of the bone marrow varied between 28.10 and 80.30% per cent.

BRUNO VASSEL (Chem. Abstr.).

The Potassium Permeability of the Myelin Sheath of Vertebrate Nerve. Harreveld, A. Van (California Inst. Technol., Pasadena). [J. Cellular Comp. Physiol., **35**, 331-40 (1950).]

The sciatic nerves of rabbits contained 140 to 220 mgm. per cent. K, the lower concentrations being in nerves of older animals. The K content remained unchanged in oxygenated Ringer solution containing glucose. In the absence of glucose a small amount of K was lost in 6 hours. Approximately 40 per cent. was lost in the absence of glucose and O₂; a similar loss occurred in Ringer solution containing 0.001 M arsenite. Loss of K from a nerve killed by formalin was moderately greater than from the asphyxiated nerve. The K diffused rapidly from nerve killed by heat which destroyed the myelin sheath. Lobster nerve, which does not have a well developed myelin sheath, and rabbit muscle lost K quickly in formalin solution.

H. L. MASON (Chem. Abstr.).

Uptake of Glutamic Acid and Glutamine by Brain and Other Tissues of the Rat and Mouse. Schwerin, Paula, Bessman, S. P., and Waelsch, Heinrich (Columbia Univ.). [J. Biol. Chem., **184**, 37-44 (1950).]

Brain tissue contains 0.01 mole free glutamic acid (I) and 0.004 mole glutamine (II) per kgm. In periods up to 1 hour intravenously injected (I) (1.2-1.3 mgm./gm. body weight) did not result in increases of brain (I) or (II); was quickly removed from blood; increased in liver and muscle through blood plasma and extracellular fluid equilibration; caused accumulation of (I) and (II) in kidney. Similarly injected (II) resulted in a slight rise in brain (II) suggesting (II) may enter the brain; liver showed rise in concentration of (II) with liberation of (I); and also caused accumulation of (I) and (II) in kidney.

GEORGE K. DAVIS (Chem. Abstr.).

The Proteins of the Gray and White Brain Substances. Palladin, A. V., and Goryukhina, T. A. (Acad. Sci. U.S.S.R., Moscow). [Fiziol. Zhur., **33**, 727-36 (1947); Chem. Zentr., 1948 (1), 777-8.].

By fractional extraction of the gray and the white brain substance with (1) water, (2) 4.5 per cent. KCl (pH 9.1), and (3) 0.1 N NaOH, 3 protein fractions were obtained from each substance. Under the same experimental conditions the protein contents of these fractions were fairly constant. The proteins of the individual fractions differed from each other in their isoelectric points, which were determined as the point of maximum precipitation of protein. The isoelectric point of the aqueous fraction was at pH 4.6. That of the KCl fraction was at pH 5.6 and that of the NaOH fraction at pH 5.2. About 30 per cent. of the total protein of the gray brain substance was extractable with water; the value was 19 per cent. for the white substance. Corresponding values were 28 per cent. (gray substance) and 23-4 per cent. (white substance) for protein extractable with KCl. The proportion of the total protein extractable with NaOH was the same for both the gray and white substance. In the gray substance 5 per cent. of the total protein was insoluble in the solvents used; 20 per cent. of the white substance was insoluble in these solvents.

M. G. MOORE (Chem. Abstr.).

Determination of the Ionic Exchange During Nervous Activity by Activation Analysis. Keynes, R. D., and Lewis P. R. (Univ. of Cambridge, Engl.). [Nature, **165**, 809-10 (1950).]

Single 200- μ Sepia (cuttlefish) axons were dissected, dried and sealed in fine quartz tubes. For activation analysis (C. A., **43**, 6537h, 9139i) batches of these tubes were irradiated in the Harwell pile together with spectroscopically pure samples of Na₂CO₃ and K₂CO₃. After irradiation the nerves were transferred to Ni dishes and counts were taken, first with a brass filter of 4.6 gm./sq. cm. for γ -radiation and then with one of 0.46 gm./sq. cm. for K⁴² β -radiation. After the standards were counted, Na and K contents were calculated. The limiting factor

in accuracy was the difficulty of measuring volume and weight of single axons reliably. Radioactivity measurements had a standard error of about 2 per cent and samples of 0.3 mgm. containing 0.3 γ Na and 3 γ K were analyzed without difficulty. The object of the experiment was to compare Na and K contents of resting nerves with those of nerves stimulated usually at 100 impulses/sec. for 20 minutes before being stored for analysis. Na content was increased from resting value of 40 millimoles/kgm. axoplasm to 130 millimoles/kgm., while K decreased from 325 millimoles/kgm. to 245 millimoles/kgm. In a series of 16 stimulated axons there was an average net entry of 3.8×10^{-12} mole Na/sq. cm. membrane/impulse and a net loss of 3.4×10^{-12} mole K/sq. cm. membrane/impulse. In axoplasm extruded from 500 μ squid axons, resting values were 46 millimoles Na/kgm. axoplasm and 323 millimoles K/kgm.; during stimulation at 200 impulses/sec. there was an entry of 3.5×10^{-12} mole Na/sq. cm./impulse and a loss of 3×10^{-12} mole K/sq. cm./impulse. These results provide further support for the theory of Hodgkins *et al.* (*J. Physiol.*, **108**, 37 (1949)) that during rising phase of nerve action potential there is considerable increase in the permeability of membrane to Na.

MARJORIE MUELLER (Chem. Abstr.).

Synchronized Recording of Brain Potentials, Muscle Action Currents and the Start of Movement in Reaction Time Experiments on Patients with "Chronic" Mental Symptoms after Carbon Monoxide Poisoning. Fellenius, V. (*Inst. of Applied Psychology, Stockholm*). [*Acta Paediat.*, **38**, 157-69 (1949) (*In English*).]

RUTH BERGGREN (Chem. Abstr.).

Relative Vagotonia. Hornykiewytch, Th. (*Univ. Strahlen Inst., Marburg a. d. Lahn, Ger.*). [*Z. ges. expit. Med.*, **115**, 404-35 (1950).]

Parasympathetic symptoms are caused by an unbalance in the acetylcholine (I)-cholinesterase (II) system. Absolute vagotonia arises when an excess of (I) is present with normal amounts of (II), while in relative vagotonia there is a normal amount of (I) and a deficiency of (II). For determination of (II) in serum: Incubate for 1 hour at 39° a mixture of 1 ml. serum and a solution of 20 mgm. (I) in 20 ml. H₂O at pH 8. Stop the hydrolysis by addition of 5 ml. 0.1 per cent. prostigmine at pH 8 and titrate the AcOH liberated with 0.01 N NaOH. The unit of (II) is that amount which liberates 1 ml. 0.01 N AcOH in 1 ml. serum in 60 minutes.

J. H. WEISBURGER) (Chem. Abstr.).

(Free) Amino Acids of Nervous Tissue. Roberts, Eugene, Frankel, Sam, and Harman, Pinckney J. (*Washington Univ., St. Louis, Mo.*). [*Proc. Soc. Exptl. Biol. Med.*, **74**, 383-7 (1950).]

Two-dimensional paper chromatograms were prepared. The brains of mice of several strains and various parts of the nervous system of rabbits were studied. The pattern of free amino acids in mouse brain does not reflect the amino acid composition of the brain as a whole. Free taurine, glutamine, cystine, serine, glycine, alanine, valine, the leucines and glutamic, aspartic, and γ -amino-butyric acids were detected consistently. Variations in these constituents with age, sex, and strain in mice are discussed. The sciatic nerve in the rabbit had considerably smaller quantities of detectable amino acids than the various parts of the central nervous system. A transplantable neuroblastoma in mice had a pattern of free amino acid similar to that found in other malignant tissues and in brains of 15-day embryos and significantly different from that found in all samples of normal mouse brain examined.

L. E. GILSON (Chem. Abstr.).

Changes in Brain pH Response to Carbon Dioxide after Prolonged Hypoxic Hyperventilation. Brown, E. B., jun. (*Univ. of Minnesota, Minneapolis*). [*J. Applied Physiol.*, **2**, 549-52 (1950).]

The CO₂ titration curves were determined for brain homogenate from 10 guinea-pigs which had been exposed to hypoxic hyperventilation for 24 hours, and for 10 normal guinea-pigs. A given pCO₂ produced a lower pH in the brain homogenate of the hyperventilated animals than it did in the controls.

THERESA MCKEE (Chem. Abstr.).

Alterations in the Central Nervous System of Vascular Origin in Carbon Disulfide Poisoning. *Vigliani, Enrico C., and Cazzullo, Carlo L. (Univ., Milan, Italy).* [*Med. lavoro*, **41**, 49-56 (1950).]

Workers who had been exposed to an atmosphere containing 0.1 to 1 mgm. CS_2 per l. for about 20 years developed asthenia, paresthesias, progressive impairment of gait, and mental deterioration. Some cases developed hemiplegias and others hypertension; 6 had signs of arteriosclerotic kidneys. All subjects were of less than 45 years of age.

A. E. MEYER (Chem. Abstr.).

The Blood-brain Barrier. II. Attempts to Influence the Passage of Substances into the Brain. *Hurst, E. Weston, and Davies, O. L. (Imperial Chem. Inds., Ltd., Manchester, Engl.).* [*Brit. J. Pharmacol.*, **5**, 147-64 (1950); cf. *C. A.*, **43**, 3110b.]

Adrenaline, pituitrin, theophylline, sodium acetate, sodium lactate, urethan, histamine, hexamine, 50 per cent. glycerol, coal gas and ether anesthesia were tested for their effect on the passage of strychnine, cocaine, picrotoxin, morphine, sulfonanilamide (I), sulfanilic acid (II), and a number of acidic, basic and triphenyl-methane dyes into the brains of mice. Visual appearance of fixed sectioned brain in the case of the dyes, mortality from the convulsant drugs, the analgesic effect of morphine and chemical determination of (I) and (II) were the criteria of altered penetration employed. None of the drugs or treatments had a consistent effect on penetration by all of the test substances; measures increasing the penetration of one substance into the brain did not necessarily increase the penetration of another chemically or physically similar substance. The results found for many combinations of test substances with different drugs or treatments are tabulated. It was found preferable to use in this type of study substances, the concentration of which in the grain, could be determined chemically.

RICHARD F. RILEY (Chem. Abstr.).

Cerebral Angiography. *Roach, John F. (Johns Hopkins Univ., Baltimore, Md.).* [*Am. J. Med. Sci.*, **219**, 559-69 (1950).]

A 35 per cent. solution of diodrast is recommended; the 70 per cent. solution should never be used for this purpose. Colloidal triiodoethyl stearate closely approximates the ideal contrast medium, if reports from Europe, where it was used before World War II, are correct; however, the drug has not been tried in North America, and attempts to obtain it from Europe or to synthesize it in the U.S. have been unsuccessful. Thorotrast is not recommended because of its radio-activity and non-excreatability.

MARION HORN PESKIN (Chem. Abstr.).

Turnover of Radioactive Phosphate Injected into the Subarachnoid Space of the Brain of the Rat. *Lindberg, O., and Ernster, L. (Wenner-Gren Inst., Stockholm).* [*Biochem. J.*, **46**, 43-7 (1950).]

After injecting intracranially P^{32} for 2 minutes, 40 per cent. is organically linked in the rat brain, and this increases to 70 per cent. after 8 hours, when the binding of the P^{32} becomes about constant. The P^{32} is found chiefly in adenosine triphosphate and in creatine phosphate. The labile phosphate is replaced at a rate (approx.) of 40% P/min./gm. brain . For blood corpuscles, liver, and muscle the rate reported is 1, 15, and 20-30 respectively.

S. MORGULIS (Chem. Abstr.).

Blood Destruction and Cerebral Damage in Hemolytic Disease of the Newborn. *Kuster, F., and Krings, H. (Med. Acad., Dusseldorf, Ger.).* [*Lancet*, **258**, 979 (1950); cf. *Goldman, E., Abhandl. preuss. Akad. Wiss. Math.-naturw. Klasse* 1913, **1** *Spatz. Arch. Psychiat. Nervenkrankh.*, **101**, 267 (1933).]

Injection of a highly concentrated (amount not stated) solution of bilirubin (I) into the carotid arteries of rabbits did not effect yellow discoloration of the brain. Cerebral icterus was brought about by a 30-minute infusion into the carotid artery of 100-150 mgm. (I)/100 ml. 5 per cent. glucose.

BARBARA R. MURRAY (Chem. Abstr.).

The Blocking Effect of Thiamine on the Superior Cervical Ganglion of the Cat. Mazzella, H., and Ferrero, N. (*Facultad med., Montevideo, Uruguay*). [*Arch. intern. pharmacodynamie*, **82**, 220-7 (1950).]

In decerebrate cats under dial anesthesia, the contraction of the nictitating membrane can be inhibited by large doses of thiamine, which prevent the stimulating effect of acetylcholine, nicotine, or K ions on the superior cervical ganglion.

M. L. C. BERNHEIM (Chem. Abstr.).

The Change in the Chromophile Substance of Nerve Cells on the Addition of Thiamine, as Determined by Ultraviolet Microscopy. Moiseev, E. A., and Ferkhmin A. A. (Pavlov Inst., Pavlovo, U.S.S.R.) [*Doklady Akad. Nauk. S.S.S.R.*, **60**, No. 1, 123-6 (1948); cf. Caspersson, C. A., **35**, 29⁸.]

Dogs were injected intramuscularly with a total of 100-1,000 mgm. of thiamine (I) (5-100 mgm. at a time). The spinal ganglia were then illuminated at 250-280 m μ . wave-length, and examined with the microscope and spectrophotometer. The cytoplasm of ganglionic cells of (I) treated dogs showed a greater ultraviolet absorption than that given by normal dog nerve cells. The increased absorption was probably caused by the nucleoproteins, which had been newly formed under the influence of (I). The pyrimidine component of (I) may participate in the synthesis of nerve cell nucleoproteins.

H. PRIESTLEY (Chem. Abstr.).

The Role of Vitamin B₁ in the Function of the Sympathetic Nervous System. (I) Enzymic Formation of Sympathin. Titaev, A. A. (*Acad. Med. Sci. U.S.S.R., Moscow*). [*Zhur. Fiziol. (J. Physiol.)*, **36**, 203-8 (1950).]

Active adrenaline may be formed from the oxidized form by the action of blood serum in the presence of thiamine *in vitro* in Ringer solution. The blood enzyme responsible for the reaction of adrenaline also causes irreversible oxidation of thiamine to thiochrome in the presence of oxidized adrenaline, which is thus reduced. Perfusion of frog heart with Ringer solution containing thiamine (5 minutes) followed by BuOH extraction shows on fluorescence examination only traces of thiochrome in a normal heart fluid, but in the presence of adrenaline a significant rise of thiochrome occurs (in frog and rabbit experiments). The result is similar on excitation of atropinized heart nerves in the presence of thiamine. Usual precipitation methods are ineffective in actual isolation of thiochrome from blood media, but extraction with iso-BuOH after precipitation of the blood by means of 1:2 EtOH appears to be satisfactory. Thiochrome itself is not an inert substance and experiments with the pure substance (by ferricyanide oxidation of thiamine *in vitro*) at 10⁻⁴-10⁻⁶ concentrations showed a definite stimulation of frog heart action, analogous to that caused by adrenaline. Mg stimulation of the activity of the thiamine-dehydrogenase is readily shown *in vitro* and *in vivo*. This enzyme system may be the possible route for the formation of sympathins *in vivo*.

G. M. KOSOLAPOFF (Chem. Abstr.).

Hypophyseal Changes Following Hypothalamic Injuries. Action of Phlorizin. Soulaïrac, A., and Desclaux, P. [*Ann. endocrinol. (Paris)*, **8**, 343-6 (1947); *Chem. Zentr.*, **1**, 588 (1948).]

In animal experiments bilateral injury to the hypothalamus caused hypophyseal degranulation, hyperphagia, and gain in weight. Phlorizin injections repressed the hyperphagia. After these injections the chromophilic cells of the anterior lobe appeared to be normally granulated. Phlorizin repressed the intestinal absorption of glucose.

M. G. MOORE (Chem. Abstr.).

Effects of Pituitary Adrenocorticotrophic Hormone (ACTH) Therapy. Electroencephalographic and Neuropsychiatric Changes in Fifteen Patients. Hoefler Paul F. A., and Glaser, Gilbert, H. (Columbia Univ.). [*J. Am. Med. Assoc.*, **143**, 620-4 (1950).]

The powerful side effects, such as significant electroencephalographic or psychiatric changes, are described, resulting from ACTH therapy.

S. MORGULIS (Chem. Abstr.).

Chemical Composition of Myelin. Brodal, A., and Harrison, R. G. [*Quart. J. Microscop. Sci.*, **89-102** (1948).]

Application of Baker's acid hematein and pyridine-extraction tests indicate the presence of phospholipides in the myelin of the central nervous system of rats and man. Probably, fibers of diameter down to at least 0.5μ have a lipide investment and the distinction between myelinated and non-myelinated fibers is arbitrary.

B. A. (Chem. Abstr.).

Alkaline Phosphatase in the Choroid Plexus. Firket, H., Heusghem, C., Gerebtzoff, M. A., and Ninane, G. (Univ. Liege, Belg.). [*Compt. rend. soc. biol.*, **143**, 1407-8 (1949).]

The choroid plexus of the rabbit and guinea-pig contains a large amount of a phosphatase with maximum activity at pH 9.5 and a small amount of another phosphatase with maximum activity at pH 4.5. L. E. GILSON (Chem. Abstr.).

Carbonic Anhydrase in the Nervous System. Kreps, E. M. (*Acad. Sci. U.S.S.R., Moscow*). [*Fiziol. Zhur.*, **36**, 97-110 (1950).]

Review with many references. The concentration of the enzyme in the brain is characteristic for the species; with increased complexity of the organism the bulk of the enzyme shifts to the cortex of the large hemispheres. Oxygen starvation leads to rise of activity of the enzyme in the brain.

G. M. KOSOLAPOFF (Chem. Abstr.).

β -Glucosidase in the Brain. Kartasheva, N. V., and Rozengart, V. I. (V. M. Bekhterev Psychoneurol. Inst., Leningrad). [*Biokhimiya*, **15**, 168-72 (1950).]

β -Glucosidase is absent in the brain of man, rabbit and cat. If sterile conditions are not maintained, the incubation of brain tissue with salicin does lead to the formation of glucose, the β -glucosidase having been supplied by contaminating micro-organisms (streptococci and staphylococci).

H. PRIESTLEY (Chem. Abstr.).

Anoxybiotic Processes in Frog Nerve. Aykut, R., and Winterstein, H. (Univ. Istanbul, Turkey). [*Arch. intern. pharmacodynamie*, **81**, 222-9 (1950).]

Nerves continuously washed in O-free Ringer solution retain their function much better than nerves in unchanged O-free Ringer solution. Addition of O causes quick recovery of the latter but not the former. Evidently the lethal substances are oxidizable and dialyzable. In O-free solutions containing NaNO_2 , exactly the reverse results are obtained.

M. L. C. BERNHEIM (Chem. Abstr.).

Allergic Encephalitis and Its Possible Relation to Human Disease. Peers, James H. (Natl. Inst. Health, Bethesda, Md.). [*Am. J. Clin. Path.*, **20**, 503-14 (1950).]

Allergic encephalitis is an inflammatory and degenerative process in the brain of animals produced by parenteral injection of homologous or heterologous brain tissue. It has considerable resemblance to human post-vaccinal encephalitis. The encephalogenic substance is connected with the phosphatide fraction of brain tissue. It is water-soluble, can be removed from rabies vaccine by treatment with $\text{Ca}(\text{OAc})_2$ and is dialyzable through a cellophane membrane.

JOHN T. MYERS (Chem. Abstr.).

Brain Metabolism in vivo. (1) *The Distribution of Lesions Caused by Cyanide Poisoning, Insulin Hypoglycemia, Asphyxia in Nitrogen and Fluoroacetate Poisoning in Rats.* Hicks, S. P. (New England Deaconess Hosp., Boston, Mass.). [*Arch. Path.*, **49**, 111-37 (1950).]

Maximum non-lethal doses of KCN to rats were selectively destructive to the white matter of the brain. Insulin and asphyxia caused different types of brain lesions, also mild heart lesions. Fluoroacetate damaged the heart and testes, but not the brain.

M. L. C. BERNHEIM (Chem. Abstr.).

Analysis of Physiological Processes Underlying Experimental Reflex Epilepsy. Krushinskii, L. V., Fless, D. A., and Molodkina, L. N. [*Zhur. Obshechi Biol.*, **11**, 104-19 (1950).]

Effects of NaBr, KBr, MgO, caffeine, strychnine and luminal were tested in rats with experimental epilepsy. Results, as compared with controls, are shown in kymographs.

JULIAN S. SMITH (Chem. Abstr.).

2. Pharmacology and Therapy.

Curarizing Agents and Experimental Epilepsy in the Rat. Quivy, D., Bertrand, Ivan, and Gayet-Hallion, Th. (*École pratique Hautes-Études, Paris*). [*Compt. rend. soc. biol.*, **143**, 1597-9 (1949).]

The two curarizing drugs, myanesin and 1,2,3tris(ethylaminoethoxy)benzene triethiodide (RP 3697, flaxedil), protected rats against lethal doses of metrazole and offered some protection against electric shock. Myanesin protected against the LD₁₀₀ of strychnine, the other drug did not. Neither protected against picrotoxin.

L. E. GILSON (Chem. Abstr.).

Action of d-tubocurarine on Nervous Centers. Arduini, A., and Zanchetti, A. (Univ. Parma, Italy). [*Boll. soc. ital. biol. sper.*, **24**, 582-3 (1948).]

d-Tubocurarine (I) has a stimulating action which is reversibly abolished by Et₂O. The effect is comparable to that obtained with equimolecular amounts of strychnine nitrate (II) (threshold concentration of (II), 1.29×10^{-3} M); however, it sets in later and lasts longer. Approximate 0.1 per cent. solutions of curare or (I) produce equivalent motor excitation.

J. H. WEISBURGER (Chem. Abstr.).

Action of Curarizing Agents on the Electroencephalogram of the Rabbit. Quivy, D., Bertrand, I., and Gayet-Hallion, T. (*Hospice Salpêtrière, Paris*). [*Arch. intern. pharmacodynamie*, **81**, 121-7 (1950).]

In non-anesthetized rabbits with no artificial respiration, d-tubocurarine causes a burst of waves of high potential but does not suppress β waves as well as does 3697 RP. Cresoxypropanediol produces an electroencephalogram resembling that of sleep.

M. L. C. BERNHEIM (Chem. Abstr.).

The Effect of d-Tubocurarine Chloride on Human Perceptivity. Kellgren, J. H., McGowan, A. J., and Wood, D. R. (Wingfield-Morris Orthopedic Hosp., Oxford, Engl.). [*Brit. Med. J.*, **2**, 898 (1946); *Chem. Zentr.*, **1**, 204 (1948)].

Intravenous injection of 5 or 7.5 mgm. of d-tubocurarine chloride produced considerable paralysis of the facial and maxillary muscles and, to a lesser degree, of the cervical and arm muscles. Neither cerebral activity nor sensitiveness to pain were influenced.

M. G. MOORE (Chem. Abstr.).

The Value of Artificial Respiration in Pentobarbital Poisoning of Rabbits. Schack, Jerome A., Goldbaum, Leo R., and Faison, Elenora D. (Army Med. Dept. Research and Graduate School, Washington, D.C.). [*Anesthesiology*, **11**, 452-4 (1950); cf. *C. A.*, **42**, 279a; **43**, 7582f.].

The rabbit will tolerate toxic doses of pentobarbital (I) providing adequate pulmonary ventilation is maintained. The (I) metabolism, as evidenced by the disappearance of (I) from the circulating blood, continues while the animal is maintained under artificial respiration. The basic importance of maintenance of adequate pulmonary ventilation in the therapy of barbiturate depression is affirmed.

RUTH BERGGREN (Chem. Abstr.).

A Method for the Prevention of Suicidal Deaths Caused by the Barbituric Acid Derivatives. Miskimon, Robert M., and Miskimon, R. Roy (1001 West Franklin Street, Richmond, Va.) [*Virginia Med. Monthly* **77**, 119-22 (1950).]

Experiments on dogs indicated that ZnSO₄ is the most constant and certain emetic both alone and in the presence of the barbituric acid derivatives. In the presence of the chosen barbiturate, the dosage of ZnSO₄ required to produce emesis

was five times the amount required for ZnSO_4 alone. This suggests that the barbiturate has some local action on either the gastric mucosa or on the nerve endings in the gastric wall. When the barbiturate was combined with ZnSO_4 the usual sedative dose of the barbiturate produced the usual amount of sedation without any evidence of nausea. With this combination an established fatal dose of the barbiturate did not even produce sedation because of complete gastric emptying by emesis. This effect was produced by ZnSO_4 even upon a full stomach. No after effects were noted. The established fatal dose of the barbiturate given alone proved fatal to these same dogs in every case.

RUTH BERGGREN (Chem. Abstr.).

Effect on Markmanship of Some Motion Sickness Preparations Containing Barbiturates and Hyoscine. Tyler, David B. (Calif. Inst. of Technol., Pasadena). [J. Applied Physiol., **1**, 737-42 (1949).]

MSP (65 mgm. amytal, 0.2 mgm. hyoscine, 0.15 mgm. atropine per capsule) had a beneficial effect on markmanship. RCN (100 mgm. niacin, 0.15 mgm. hyoscine, 0.4 mgm. hyoscyamine per capsule), or V 12 (130 mgm. ethyl (2-methylallyl)thiobarbituric acid) had no significant effect. MSP in doses recommended as a preventive of motion sickness can be safely given to military personnel.

THERESA MCKEE (Chem. Abstr.).

Effect of Some Surface-active Agents on the Action of Barbiturates. Cole, Versa V., Hulpieu, H. R., and Hopper, S. H. (Indiana Univ., Indianapolis). [Proc. Soc. Exptl. Biol. Med., **73**, 554-7 (1950).]

The duration of hypnosis by pentobarbital-Na in mice was increased by all of the 11 surface-active agents (anionic, cationic and nonionic) tested. Di-Na-di-butylhydroxybiphenyldisulfonate (Aresklene 400) (I), the only one studied in other animals, increased the duration of pentobarbital hypnosis in rats and rabbits, but not in dogs. In mice thiopental-Na showed an increase in effect with some but not all of the surface-active agents. (I) increased the activity of thiopental apparently by decreasing its rate of destruction in the body. The time of onset of hypnosis was decreased by (I) given with barbital-Na in mice, rabbits and dogs but not in rats. The duration was not affected. Six of 10 other agents had the same effect on onset of hypnosis in mice.

L. E. GILSON (Chem. Abstr.).

Hyperkinesis of Mesencephalic Origin, which Arises in Frogs under Barbiturate Narcosis. Markova, I. V. (Leningrad Pediat. Inst.). [Fiziol. Zhur. (J. Physiol.), **36**, 161-5 (1950).]

In the initial stage of barbiturate narcosis frogs exhibit enhanced mobility of two types; free motion (crawling, jumping) and a hyperkinesis which arises after the primary stages and which depends on intact condition of mesencephalon; this is exhibited in the form of inability of the animal to return from dorsal position, relaxation of skeletal musculature and lengthening of the latent period of reflex motions. As a result, the frog may be used as a test object for study of drugs which affect either the frontal sections of the brain or primarily the mid-brain locations.

G. M. KOSOLAPOFF (Chem. Abstr.).

Identification of Barbituric Acid in Urine in the Presence of Sulfonamides. Mohrschulz, Wilhelm (Stadt. Krankenhaus, Munich, Ger.). [Suddeut. Apoth.-Ztg., **90**, 335-6 (1950).]

Sulfonamides of their Na salts when present in urine give false positive tests for barbituric acid with Zwikker's reaction (cf. C. A., **26**, 396).

EDWARD H. SHEERS (Chem. Abstr.).

Action of Certain Substances with Narcotic and Stimulating Action on the Subsequent Discharges as a Result of Stimulation of Afferent and Pyramidal (Descending) Fibers. Zakusov, V. V. (1st Pavlov Med. Inst., Leningrad). [Fiziol. Zhur. (J. Physiol.), **36**, 184-90 (1950).]

Application of rapidly interrupted d.c. to the afferent (by means of chlorinated Ag electrodes) and pyramidal (by means of Pt electrodes) fibers of rabbits with administration of the various drugs, showed that: At low doses (0.1 gm./kgm.)

urethan weakens and shortens the subsequent discharges to a greater extent after stimulation of the afferent fibers than that of the pyramidal ones; at larger doses the difference vanishes. Subtoxic level of scopolamine affects only the subsequent discharges resulting from stimulation of the pyramidal fibers and has no effect on the results with stimulation of afferent fibers. Strychnine and corazole enhance and lengthen the discharges in both instances, strychnine being more effective with "afferent" stimulation. Hence narcotics depress excitation processes in the central nervous system caused by external stimuli, while analeptics sustain them.

G. M. KOSOLAPOFF (Chem. Abstr.).

The Sympathomimetic Depressor Agents: A Review. Ahlquist, Raymond P., and Hensen, James P. (Med. Coll. of Georgia, Augusta). [*J. Am. Pharm. Assoc.*, **39**, 382-8 (1950).]

A review of the depressor activities and acute toxicity of 87 depressor sympathomimetic amines.

DAVID B. SABINE (Chem. Abstr.).

Absence of a Toxic Effect of Folic Acid on the Central Nervous System of Persons Without Pernicious Anemia. Harvey, Earle A., Howard, Isabel, and Murphy, Wm. P. (Harvard Med. School, Boston, Mass.) [*New Engl. J. Med.*, **242**, 446-7 (1950).]

No spinal cord or peripheral-nerve damage occurred in 40 subjects with hypochromic anemia during treatment with 20 mgm. folic acid daily for 3-12 months. Folic acid did not alter the blood of persons with normal hemoglobin levels or those with slight to moderate anemia. The rate of hemoglobin increase after the use of ferrous sulfate plus folic acid in 3 patients with moderately severe anemia was not definitely more rapid than would have been expected from ferrous sulfate alone. An increase of appetite and a slight gain in weight occurred in a few subjects during the first few weeks of treatment only.

MARION HORN PESKIN (Chem. Abstr.).

Niacinamide in Bromide Intoxication. Harris, R. S., and Derian, P. S. (Univ. of Virginia Med. School, Charlottesville). [*Southern Med. J.*, **42**, 973-8 (1949).]

Chronic Br intoxication shows marked parallels in symptomatology with the pellagra syndrome. In experiments on 3 groups of dogs, Group I was placed on a black tongue-inducing diet; Group II was maintained at a level of 300 mgm. per cent. blood Br; Group III was placed on a Br régime plus massive doses of niacinamide. The urinary excretion of total coproporphyrins was increased in Groups I and II. Group III dogs failed to show increased urinary porphyrins or any of the other associated signs and symptoms of bromism. Six patients with bromism were presented in whom coproporphyrin excretion was above normal. Clearance of symptoms was rapid (average 5 days) in two of the patients receiving 600-750 mgm. niacinamide per day in conjunction with NaCl therapy and in the remaining 4 patients given niacinamide only. A working hypothesis is advanced postulating destruction or inhibition of coenzyme I and II by a high level of serum Br or a reduced blood Cl.

RUTH BERGGREN (Chem. Abstr.).

Effects of a New Quarternary Amine and a New Imidazoline Derivative on the Autonomic Nervous System. Longino, F. H., Grimson, K. S., Chittum, J. R., and Metcalf, B. H. (Duke Univ., Durham, N.C.). [*Surgery*, **26**, 421-34 (1949); cf. *C. A.*, **43**, 5496e.]

The compounds, 2,6-dimethyl-(1),(1)-diethylpiperidinium bromide, and 2-(N-p-tolyl-N-(m'-hydroxyphenyl)aminoethyl) imidazoline-HCl were effective and well tolerated.

RUTH BERGGREN (Chem. Abstr.).

Action of Myanesin on Medullary Synaptic Transmission in the Acute Spinal Dog. Baisset, A., Laporte, Yves, and Grezes-Rueff, F. (Univ. Toulouse, France). [*Compt. rend. soc. biol.*, **143**, 1515-17 (1949).]

The drug depresses transmission. Action of 1,2,3-tris(diethylaminoethoxy) benzene triethiodide (*Ibid.*, 1518-19). The Compound has no effect on medullary synaptic transmission even in doses four times as great as are sufficient to block neuromuscular transmission.

L. E. GILSON (Chem. Abstr.).

Drugs Accelerating and Inhibiting Alcoholic Intoxication. Chauchard, Paul, Mazoué, Henriette, and Lecoq, Raoul (*École hautes études, Paris*). [*Compt. rend. soc. biol.*, **143**, 1550-3 (1949).]

Apomorphine, tetraethylthiuram disulfide, and 1-octanol augment the effect of EtOH on chronaxia in the rat, while KSCN and 1-phenyl-2-aminopropane decrease the effect. MgSO₄ given subcutaneously or intravenously has no influence.

L. E. GILSON (Chem. Abstr.).

Treatment of Alcoholism with Antabuse (Tetraethyl-thiuram disulfide). Carratala, Rogelio. [*Rev. asoc. med. argentina*, **64**, 220-1 (1950).]

Ingestion of EtOH after antabuse results in an increase in acetaldehyde in the blood. In rabbits this increase is 4-11 times that produced by EtOH alone. The intravenous injection of 0.03-0.12 gm./kgm. acetaldehyde produces transient narcosis in dogs, cats and rabbits; 0.25-0.35 gm./kgm. produces death by respiratory arrest.

L. E. GILSON (Chem. Abstr.).

Disappearance of the Convulsant Activity of Brucine when Converted to its Methiodide. Busquet, H., and Vischniac, Ch. [*Compt. rend. soc. biol.*, **144**, 53-4 (1950).]

Brucine methiodide is quite toxic to experimental animals, but has little or no convulsant activity as compared with brucine.

L. E. GILSON (Chem. Abstr.).

Effect of Some Anticonvulsant Agents on Agene-induced Convulsions in Dogs. Belford, J., and Bonmycastle, D. D. (Yale Univ.). [*J. Pharmacol. Exptl. Therap.*, **99**, 325-8 (1950).]

Without producing signs of toxicity, phenobarbital can prevent the occurrence of convulsions in dogs receiving agenized zein at a dosage level which induces convulsions in 100 per cent. of controls. There is some evidence that diphenylhydantoin has a positive synergistic action with the convulsant action of agenized zein. Trimethadione protects from the convulsions, but only at levels which result in toxic effects. Paradione affords some protection against the convulsions without toxic effects.

L. E. GILSON (Chem. Abstr.).

Metrazole Activation of Acetylcholine-treated Cerebral Cortex. Forster, Francis M., and Madow, Leo (Jefferson Med. Coll., Philadelphia, Pa.). [*Am. J. Physiol.*, **161**, 426-9 (1950).]

Cerebral cortex treated with acetylcholine topically is activated by parenteral injections of metrazole in doses below the threshold of untreated cortex. With careful control the seizure discharge can be limited to the area of acetylcholine application. These results of metrazole activation are similar to those seen in patients with focal epileptogenic lesions.

Experimental Sensory-induced Seizures. [*Ibid.*, 430-4.]

Sensory-induced seizures in experimental animals can be induced by the application of acetylcholine to a sensory cortex and administration of the appropriate stimulus during metrazole activation. These observations are correlated with clinical studies in sensory-induced epilepsy.

E. D. WALTER (Chem. Abstr.).

Anticonvulsant Action of Isopropanol. Schaffarzick, Ralph W. (Stanford Univ. Med. School, San Francisco). [*Proc. Soc. Exptl. Biol. Med.*, **74**, 211-15 (1950).]

Rats and rabbits were given (by stomach tube) the optimal single dose of iso-PrOH, 1250 mgm./kgm. Larger doses produce ataxia. Analyses of blood iso-PrOH and Me₂CO in relation to elevation of cortical threshold to electric stimulation indicate that the alcohol itself is responsible for the anticonvulsant effect, although the acetonemia may contribute. 2-Butanol, 3-pentanol, and 2-methyl-2-butanol effectively raised the cortical threshold, with or without acetonemia. Iso-PrOH antagonized the convulsive action of metrazole and thujone (cedar-leaf oil), but was not effective against picrotoxin.

L. E. GILSON (Chem. Abstr.).

Deoxycortone with Ascorbic Acid in Mental Disorders. Some Clinical and Laboratory Findings. Cranswick, E. H., and Hall, T. C. [*Lancet*, **258**, 540-3 (1950).]

Mental cases with symptoms of less than one year's duration showed euphoric reactions after administration of deoxycortone and ascorbic acid. Response to the treatment was associated with decrease in eosinophils and changes in the urinary uric acid/creatinine ratio.

BARBARA R. MURRAY (Chem. Abstr.).

Tannic Acid and Adrenaline and Sympathetic Nerve Activity. Konzett, H (Edinburgh Univ., Scot.). [*Arch. intern. pharmacodynamie*, **81**, 251-7 (1950).]

Tannic acid (1 : 10,000,000) enhances the effect of adrenaline on rabbit intestine and uterus. Given intravenously, it increases the effect of adrenaline on the nictitating membrane and blood pressure of cats. The acid alone has no effect on isolated organs or *in vivo*.

M. L. C. BERNHEIM (Chem. Abstr.).

The Effects of Intravenously Administered Aminophylline on Cerebral Circulation and Metabolism in Man. Wechsler, Richard L., Kleiss, Lee M., and Kety, Seymour S. (Univ. of Pennsylvania, Philadelphia). [*J. Clin. Invest.*, **29**, 28-30 (1950).]

The effects of administration of therapeutic amounts of aminophylline on the blood gases, blood pH, cerebral blood flow, cerebral O consumption, and cerebrovascular resistance was studied in 10 subjects. It produced a marked constriction of cerebral vessels and a real anoxia of cerebral tissue. Some individuals react with an increased cerebral O consumption accompanied by disturbing symptoms and anxiety.

JOHN T. MYERS (Chem. Abstr.).